# Introduction

## Role of the *WHO monographs on selected medicinal plants*

The first volume of the *WHO monographs on selected medicinal plants*, containing 28 monographs, was published in 1999. It is gratifying that the importance of the monographs is already being recognized. For example, the European Commission has recommended volume 1 to its Member States as an authoritative reference on the quality, safety and efficacy of medicinal plants. The Canadian Government has also made a similar recommendation. Furthermore, as hoped, some of WHO's Member States, such as Benin, Mexico, South Africa and Viet Nam, have developed their own monographs based on the format of the WHO monographs.

The monographs are not only a valuable scientific reference for health authorities, scientists and pharmacists, but will also be of interest to the general public. There can be little doubt that the WHO monographs will continue to play an important role in promoting the proper use of medicinal plants throughout the world.

## Preparation of monographs for volume 2

At the eighth International Conference on Drug Regulatory Authorities (ICDRA) held in Manama, Bahrain, in 1996, WHO reported the completion of volume 1 of the WHO monographs. Member States requested WHO to continue to develop additional monographs. As a consequence, preparation of the second volume began in 1997.

During the preparation, the number of experts involved, in addition to members of WHO's Expert Advisory Panel on Traditional Medicine, significantly increased compared to that for volume 1. Similarly, the number of national drug regulatory authorities who participated in the preparation also greatly increased. This global network of active collaborators facilitated wider access to the scientific references and information, thus increasing both the quality and quantity of the monographs. These combined efforts greatly improved the efficiency of the preparation. As for volume 1, the monographs were drafted by the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago, United States of America.

The Second WHO Consultation on Selected Medicinal Plants was held in Ravello-Salerno, Italy, in March 1999 to review and finalize the draft monographs. Twenty experts and drug regulatory authorities from WHO Member

States participated (see Annex 1). Following extensive discussion, 30 of 31 draft monographs were approved for volume 2. At the subsequent ninth ICDRA in Berlin, Germany in April 1999, the 30 draft monographs were presented, and Member States requested WHO to publish them as soon as possible.

## Purpose and content of the monographs

The purpose of the monographs was clearly explained in the introduction to volume 1, and it is unnecessary to repeat it here. However, it is important to emphasize that the word "monograph", as appears in the title, is used as a technical term only. These monographs are not intended to be official pharmacopoeial monographs.

It should also be stressed that this publication is not intended to replace official compendia such as pharmacopoeias, formularies or legislative documents. Furthermore, the descriptions included in the section on medicinal uses should not be taken as implying WHO's official endorsement or approval. They merely represent the systematic collection of scientific information available at the time of preparation, for the purpose of facilitating information exchange.

A description of selected sections of the monographs is given in the *General technical notices*. For easy reference, two cumulative indexes are also provided as annexes. Annex 2 lists the monographs in alphabetical order of the plant name, while Annex 3 is according to the plant material of interest.

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# General technical notices

These WHO monographs are not pharmacopoeial monographs. Their purpose is to provide scientific information on the safety, efficacy and quality control/quality assurance of widely used medicinal plants, in order to facilitate their appropriate use in WHO's Member States; to provide models to assist WHO's Member States in developing their own monographs or formularies for these and other herbal medicines; and to facilitate information exchange among WHO's Member States.

The format used for volume 2 essentially follows that of volume 1. However, to keep relevant sections together, *Geographical distribution* now precedes *Description*; and *Dosage forms* appears before *Posology*.

The *Definition* describes the identity of the plant material of interest and the Latin binomial name of the source plant, the binomial name being the most important criterion in quality assurance of the crude drug. Latin pharmacopoeial synonyms and vernacular names, listed in the sections *Synonyms* and *Selected vernacular names*, respectively, are those names used in commerce or by local consumers. The monographs place outdated botanical nomenclature in the synonyms category, based on the *International rules of nomenclature*.

The vernacular names listed are a selection of names from individual countries worldwide, in particular from areas where the medicinal plant is in common use. The lists are not complete, but reflect the names found at the time of preparation in official monographs, reference books and the Natural Products Alert (NAPRALERT) database (a database of literature from around the world on ethnomedical, biological and chemical information on medicinal plants, fungi and marine organisms, located at the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago, USA).

A detailed botanical description (in *Description*) is intended for quality assurance at the stages of production and collection of the source plant, whereas the detailed description of the specific plant part used (the crude drug)—in *Plant material of interest*—is for quality assurance at the manufacturing and commercial stages. *Geographical distribution* is not normally found in official compendia, but it is included here to provide additional quality assurance information.

*General identity tests*, *Purity tests* and *Chemical assays* are all normal compendial components included under those headings in these monographs. Where purity tests do not specify accepted limits, those limits should be set in accordance with requirements of the respective national health authorities.

Each medicinal plant and crude drug contains active or major chemical constituents with a characteristic profile that can be used for chemical quality

control and quality assurance. These constituents are described in the section *Major chemical constituents*.

Descriptions included in the section on *Medicinal uses* should not be taken as implying WHO's official endorsement or approval. They merely represent the systematic collection of scientific information available at the time of preparation, for information exchange. Medicinal uses are categorized as uses supported by clinical data; uses described in pharmacopoeias and in traditional systems of medicine; and uses described in folk medicine, not yet supported by experimental or clinical data.

The first category includes medicinal indications that are well established in some countries and have been validated by clinical studies documented in the scientific literature. The clinical trials may have been controlled, randomized, double-blind studies, trials without controls, cohort studies, or well-documented observations of therapeutic applications.

The second category includes medicinal uses that are well established in many countries and are included in official pharmacopoeias or national monographs. Well-established uses having a plausible pharmacological basis and supported by older studies that clearly need to be repeated are also included. The references cited provide additional information useful in evaluating specific herbal preparations. The uses described should be reviewed by local experts and health workers for their applicability in the local situation.

The third category refers to indications described in unofficial pharmacopoeias and other literature, and to traditional uses. The appropriateness of these uses could not be assessed, owing to a lack of scientific data to support the claims. The possible uses of these remedies must be carefully considered in the light of therapeutic alternatives.

The *Experimental pharmacology* section includes only the results of investigations that prove or disprove the cited medicinal uses. Abbreviated details of the best-performed studies have been included in this section. Other published experimental data that are not associated with the medicinal uses have not been included to avoid confusion.

The details included in the section on *References* have been checked against the original sources wherever possible. However, in some cases, details are missing as the original sources were not available. For non-English language references, the title is given in the original language, except in cases where an English summary is available.

# Radix Althaeae

## Definition

Radix Althaeae consists of the dried roots of *Althaea officinalis* L. (Malvaceae) (*1–4*).

## Synonym

*Malva officinalis* L. (*5*).

## Selected vernacular names

Altea, altee, althea, bardul khatmi, benefischi, bismalva-hibiscus, blanca malva, bon visclo, bourdon de St Jacques, Eibisch, Eibischwurzel, erva molle, guimauve, Heilwurz, hobbiza, Ibischwurz, khairi, khatmi, korzén prawóslazu, marshmallow, marshmallow root, malvaccioniu, malvavisco, marmolone, molotta, Moorish mallow, orvosiziliz gyökér, racine d'althée, racine de guimauve, Sammetpappel, sauvage, Schleimwurzel, suzmool, sweet weed, white mallow, wymote (*3*, *6–8*).

## Geographical distribution

Indigenous to western Asia and Europe, and is naturalized in the United States of America (*9*, *10*). Roots are obtained from commercially cultivated plants that are at least 2 years old and harvested in the autumn (*6*, *10*).

## Description

A perennial herb with erect, woody stems, 60–120 cm high. Leaves alternate, ovate to slightly cordate, serrate, velvety, large, occasionally 3-lobed. Flowers pale pink, axillary, the calyx of each surrounded by a 6–9 cleft involucre. Fruit a set of cocci united into a ring (*11*).

## Plant material of interest: dried roots

### *General appearance*

Cylindrical or tapering, slightly twisted roots, up to 2 cm thick, with deep longitudinal furrows. Outer surface greyish-brown, bearing numerous rootlet scars. Fracture externally fibrous, internally rugged and granular; section shows

a thick, whitish bark with brownish periderm, separated by a well-marked, brownish cambium from the white xylem; stratified structure of the bark and radiate structure of xylem become more distinct when moist. Peeled root has greyish-white finely fibrous outer surface; cork and external cortical parenchyma absent (*2*).

### *Organoleptic properties*

Odour: faint, aromatic; taste: mucilaginous (*1*).

### *Microscopic characteristics*

Phloem with numerous long, thin-walled, non-lignified fibres arranged in tangential groups alternating with groups of sieve tissue, with a ground tissue of thin-walled parenchyma; xylem containing reticulate or scalariform thickening and bordered pits accompanied by lignified tracheids, a small amount of lignified parenchyma and occasional small groups of fibres with only the middle lamella lignified; xylem and phloem transversed by numerous non-lignified medullary rays, mostly uniseriate; majority of parenchyma cells of the phloem and medullary rays contain abundant small starch grains which are mostly simple, spherical to ovoid, occasionally 2–3 compound, with a well-marked circular or slit-shaped hilum; some of these parenchyma cells contain cluster crystals of calcium oxalate 20–40 µm in diameter, while others exist as idioblasts containing mucilage (*1*).

### *Powdered plant material*

Brownish-grey (unpeeled root) or whitish (peeled root). Fragments of colourless, mainly unlignified, thick-walled fibres with pointed or split ends; fragments of reticulate or scalariform thickening and bordered pits; cluster crystals of calcium oxalate about 20–35 µm, mostly 25–30 µm, in diameter; parenchyma cells containing mucilage; fragments of cork with thin-walled, tabular cells in the powdered material from the unpeeled root. Numerous starch grains, 3–25 µm in diameter, with occasionally a longitudinal hilum; starch grains mostly simple, a few being 2–4 compound (*2*).

## General identity tests

Macroscopic and microscopic examinations (*1*, *2*).

## Purity tests

### *Microbiology*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

### *Foreign organic matter*
Not more than 2% of brown, deteriorated drug and not more than 2% of cork in the peeled root (*2*).

### *Total ash*
Not more than 6% in the peeled root and not more than 8% in the unpeeled root (*2*).

### *Acid-insoluble ash*
Not more than 3% in the peeled root (*1*).

### *Water-soluble extractive*
Not less than 22% (*1*).

### *Loss on drying*
Not more than 12% (*2*).

### *Swelling index*
Not less than 10 (*2*).

### *Pesticide residues*
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*2*). For other pesticides, see the *European pharmacopoeia* (*2*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*13*).

### *Heavy metals*
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

### *Radioactive residues*
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

### *Other purity tests*
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

## Chemical assays
Not less than 10% total mucilage in the peeled root as determined by gravimetric analysis (*14*).

## Major chemical constituents

The mucilage content ranges from 10 to 20% and consists of a mixture of acidic galacturonorhamnans, neutral glucans and neutral arabinogalactans (*6, 8, 9, 15–17*).

## Medicinal uses

### Uses supported by clinical data

None.

### Uses described in pharmacopoeias and in traditional systems of medicine

As a demulcent for symptomatic treatment of dry irritable coughs and irritations of oral and pharyngeal mucosa and as an emollient for wounds and dry skin (*8, 18–23*). Also used in cough mixtures to mask the bitter or pungent taste of other drugs (*16*).

### Uses described in folk medicine, not supported by experimental or clinical data

Treatment of asthma, cystitis, dysentery and irritations of the gastric mucosa (*7*).

## Pharmacology

### Experimental pharmacology

The demulcent effects of Radix Althaeae are due to its high content of polysaccharide hydrocolloids, which form a protective coating on the oral and pharyngeal mucosa, soothing local irritation and inflammation (*24*).

#### Anti-inflammatory activity

A polysaccharide fraction (500 µg/ml) isolated from a root extract had anticomplement activity in human serum in vitro (*25*). Aqueous extracts of the roots stimulated phagocytosis, and the release of oxygen radicals and leukotrienes from human neutrophils in vitro (*26*). The aqueous extract also induced the release of cytokines, interleukin-6 and tumour necrosis factor from human monocytes in vitro, thereby exhibiting anti-inflammatory and immunostimulant activity (*26*). Intraperitoneal administration of isolated mucilage polysaccharides to mice (10 mg/kg body weight) induced a 2.2-fold increase in the phagocytic activity of macrophages as measured by the colloidal carbon clearance test (*27*). However, intragastric administration of an 80% ethanol extract of the roots to rats (100 mg/kg body weight) did not inhibit carrageenan-induced footpad oedema (*28*).

Weak inhibition (17%) of mucociliary transport in isolated, ciliated epithelium of the frog oesophagus was demonstrated after treatment of the isolated tissues with 200 µl of an aqueous root macerate (6.4 g/140 ml) (*29*).

**Antitussive activity**

Intragastric administration of a polysaccharide fraction, isolated from an aqueous root extract, to cats (50 mg/kg body weight) suppressed the intensity and the frequency of coughs induced by mechanical irritation of laryngopharyngeal and tracheobronchial mucosa (*30*). The antitussive activity of this polysaccharide fraction (50 mg/kg body weight) was as effective as Syrupus Althaeae (1.0 g/kg body weight), and more effective than prenoxdiazine (30 mg/kg body weight) (*30*).

### *Clinical pharmacology*

None.

## Contraindications

No information available.

## Warnings

No information available.

## Precautions

### *Drug interactions*

Simultaneous administration of Radix Althaeae may delay the absorption of other drugs (*8*).

### *Other precautions*

No information available on general precautions or precautions concerning drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Radix Althaeae should not be administered during pregnancy or lactation or to children without medical supervision.

## Adverse reactions

No information available.

## Dosage forms

Peeled or unpeeled, broken, chopped or powdered crude drug (*1, 2*) and galenical preparations thereof. Store in a well-closed container, protected from light (*2*).

## Posology

(Unless otherwise indicated)

For dry cough, oral or pharyngeal irritation: 0.5–3.0 g of crude drug as an aqueous, cold macerate (*14, 19, 20, 31*) or 2–8 ml of syrup (*20, 22, 32*), which may be repeated up to a daily dose of 15 g of crude drug. For gastric irritation: 3–5 g of crude drug as an aqueous, cold macerate up to three times daily (*19, 20, 31*).

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# Herba Andrographidis

## Definition

Herba Andrographidis consists of the dried aerial parts of *Andrographis paniculata* (Burm. f.) Nees (Acanthaceae) (*1–3*).

## Synonyms

*Justicia latebrosa* Russ., *J. paniculata* Burm. f., *J. stricta* Lam. ex Steud. (*3*, *4*).

## Selected vernacular names

Akar cerita bidara, alui, Andrographidis Kraut, bidara, bhoonimba, bhuinimo, bhulimb, bhuninba, charayeta, charayetha, charita, cheranta, cherota, chiraita, chiretta, chuan-hsin-lien, chuān-xīn-lián, công công, faathalaaichon, fathalaai, fathalaichon, fathalaijone, halviva, herba sambiloto, hinbinkohomba, I-chien-hsi, kalafath, kalmegh, kan-jang, kariyat, khee-pang-hee, king of bitters, kiriathu, kirta, kiryata, kiryato, lanhelian, mahatikta, mahatita, naelavemu, nay-nahudandi, nelavemu, quasab-uz-zarirah, rice bitters, sambilata, sambiloto, senshinren, sinta, xuyên tâm liên, yaa kannguu yijianxi (*1*, *2*, *5–11*).

## Geographical distribution

Widely found and cultivated in tropical and subtropical Asia, south-east Asia and India (*6*, *8*, *10*).

## Description

A herbaceous annual, erect, up to 1 m high; stem acutely quadrangular, much branched. Leaves simple, opposite, lanceolate, glabrous, 2–12 cm long, 1–3 cm wide; apex acute; margin entire, slightly undulate, upper leaves often bractiform; petiole short. Inflorescence patent, terminal and axillary in panicle, 10–30 mm long; bract small; pedicel short. Calyx 5-particle, small, linear. Corolla tube narrow, about 6 mm long; limb longer than the tube, bilabiate; upper lip oblong, white with a yellowish top; lower lip broadly cuneate, 3-lobed, white with violet markings. Stamens 2, inserted in the throat and far exserted; anther basally bearded. Superior ovary, 2-celled; style far exserted. Capsule erect, linear-oblong, 1–2 cm long and 2–5 mm wide, compressed, longitudinally furrowed on broad faces, acute at both ends, thinly glandular-hairy. Seeds small, subquadrate (*1–3*, *5*, *10*).

## Plant material of interest: dried aerial parts

### *General appearance*

Mixture of broken, crisp, mainly dark green lanceolate leaves and quadrangular stems; capsule fruit and small flowers occasionally found (*1*, *3*). Stem texture fragile, easily broken; leaves simple, petiole short or nearly sessile, lanceolate or ovate-lanceolate, with acuminate apex and cuneate-decurrent base, lamina crumpled and easily broken (*2*).

### *Organoleptic properties*

Odour: slight, characteristic; taste: intensely bitter (*1–3*, *9*).

### *Microscopic characteristics*

Leaf upper epidermis: stomata absent, glandular trichomes present, unicellular and multicellular trichomes rare, cystoliths fairly large; lithocysts large (27–30 μm thick, 96–210 μm long and up to 49 μm wide); columnar palisade cells; collenchyma in midrib beneath epidermis; parenchyma cells spongy; vascular bundles of lignified xylem in the upper part and lignified phloem in the lower part; spiral, scalariform and reticulate vessels. Leaf lower epidermis: a layer of wavy-walled cells; stomata diacytic; trichomes up to 36 μm in diameter and 180 μm long, and cystoliths present. Stem: epidermis has glandular and non-glandular trichomes. Collenchyma dense at the corners of stems; parenchyma contains chloroplastids. Endodermis composed of a layer of thick-walled cells. Wood with spiral, scalariform and pitted xylem vessels; pith composed of large parenchyma cells. Small acicular crystals of calcium oxalate occur in the pith and cortical cells of stem and leaf (*1–3*, *8*).

### *Powdered plant material*

Leaf fragments in surface view show upper epidermis with underlying palisade and cystoliths, lower epidermis with underlying palisade cells with stomata, cystoliths and glandular trichomes. Leaf fragments in sectional view show upper epidermis with palisade cells, spongy parenchyma cells, vascular bundles; and lower epidermis with bundles of xylem associated with fibres; fragments of spiral, scalariform, reticulate and pitted vessels; fragments of epidermal cells from midrib; fragments of parenchyma cells in transverse and longitudinal sections. Bundles of fibres. Fragments of epidermal cells from stem with stomata, cystoliths and glandular trichomes. Scattered cystoliths; scattered unicellular and multicellular trichomes, mostly from epidermal cells in fruit walls; scattered glandular trichomes from bundles of fibres in fruit wall; scattered pollen grains (*1*).

## General identity tests

Macroscopic and microscopic examinations, chemical tests, and thin-layer chromatography for the presence of diterpene lactones (*1–3*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

### *Chemical*

Not less than 6% of total diterpene lactones, calculated as andrographolide (*1*, *3*).

### *Foreign organic matter*

Not more than 2% (*1*, *3*).

### *Acid-insoluble ash*

Not more than 2% (*1*, *3*).

### *Water-soluble extractive*

Not less than 18% (*1*, *3*).

### *Alcohol-soluble extractive*

Not less than 13% using 85% ethanol (*1*, *3*).

### *Loss on drying*

Not more than 10% (*1*).

### *Pesticide residues*

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

### *Heavy metals*

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

### *Radioactive residues*

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

### *Other purity tests*

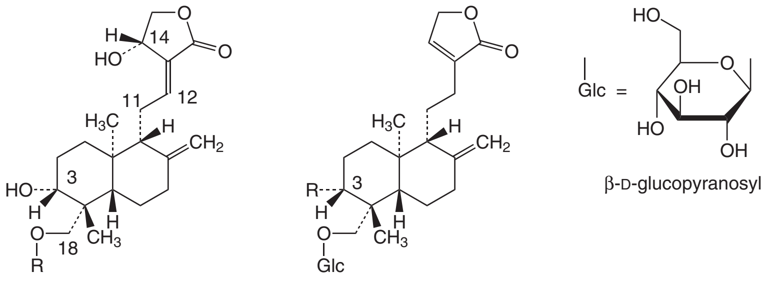
Total ash test to be established in accordance with national requirements.

## Chemical assays

Chemical and thin-layer chromatography methods are used for qualitative analysis of andrographolide diterpene lactones (*1, 2*). Titrimetric (*1*) and high-performance liquid chromatography (*15*) methods are available for quantitative analysis of total diterpene lactones.

## Major chemical constituents

The major constituents are diterpene lactones (free and in glycosidic forms) including andrographolide, deoxyandrographolide, 11,12-didehydro-14-deoxyandrographolide, neoandrographolide, andrographiside, deoxyandrographiside and andropanoside (*1, 3, 6, 7, 9, 16*). The structures of andrographolide and related diterpene lactones are presented below.




andrographolide R = H
andrographiside R = Glc

neoandrographolide R = H
andropanoside R = OH

## Medicinal uses

### *Uses supported by clinical data*

Prophylaxis and symptomatic treatment of upper respiratory infections, such as the common cold and uncomplicated sinusitis (*17–19*), bronchitis (*6, 9*) and pharyngotonsillitis (*20*), lower urinary tract infections (*21*) and acute diarrhoea (*22, 23*).

### *Uses described in pharmacopoeias and in traditional systems of medicine*

Treatment of bacillary dysentery, bronchitis, carbuncles, colitis, coughs, dyspepsia, fevers, hepatitis, malaria, mouth ulcers, sores, tuberculosis and venomous snake bites (*1, 2, 6, 7, 10, 16, 24–27*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of colic, otitis media, vaginitis, pelvic inflammatory disease, chickenpox, eczema and burns (*6, 7*).

# Pharmacology

## Experimental pharmacology

### *Antibacterial activity*

An ethanol extract of the leaves inhibited the growth in vitro of *Escherichia coli* and *Staphylococcus aureus* (*28*). A 50% methanol extract of the leaves inhibited growth in vitro of *Proteus vulgaris* (*29*). However, no in vitro antibacterial activity was observed when dried powder from the aerial parts was tested against *E. coli*, *Staphylococcus aureus*, *Salmonella typhi* or *Shigella* species (*30*).

### Anti-human immunodeficiency virus (HIV) activity

Aqueous extracts of the leaves inhibited HIV-1 infection and replication in the lymphoid cell line MOLT-4 (*31*). A hot aqueous extract of the aerial parts reduced the percentage of HIV antigen-positive H9 cells (*32*). Dehydroandrographolide inhibited HIV-1 and HIV-1 (UCD123) infection of H9 cells at 1.6 μg/ml and 50 μg/ml, respectively, and also inhibited HIV-1 infection of human lymphocytes at 50 μg/ml (*33*). A methanol extract of the leaves suppressed syncytia formation in co-cultures of uninfected and HIV-1-infected MOLT cells (median effective dose [$ED_{50}$] 70 μg/ml) (*34*).

### Immunostimulatory activity

Intragastric administration of an ethanol extract of the aerial parts (25 mg/kg body weight) or purified andrographolides (1 mg/kg body weight) to mice stimulated antibody production and the delayed-type hypersensitivity response to sheep red blood cells (*35*). The extract also stimulated a non-specific immune response in mice, measured by macrophage migration index, phagocytosis of [$^{14}$C]leucine-labelled *E. coli*, and proliferation of splenic lymphocytes (*35*). The extract was more effective than either andrographolide or neoandrographolide alone, suggesting that other constituents may be involved in the immunostimulant response (*35*).

### Antipyretic activity

Intragastric administration of an ethanol extract of the aerial parts (500 mg/kg body weight) to rats decreased yeast-induced pyrexia (*36*). The extract was reported to be as effective as 200 mg/kg body weight of aspirin, and no toxicity was observed at doses up to 600 mg/kg body weight (*36*). Intragastric administration of andrographolide (100 mg/kg body weight) to mice decreased brewer's yeast-induced pyrexia (*37*). Intragastric administration of deoxyandrographolide, andrographolide, neoandrographolide or 11,12-didehydro-14-deoxyandrographolide (100 mg/kg body weight) to mice, rats or rabbits reduced pyrexia induced by 2,4-dinitrophenol or endotoxins (*6*, *38*).

### Antidiarrhoeal activity

Herba Andrographidis has antidiarrhoeal activity in situ (*39*, *40*). An ethanol, chloroform or 1-butanol extract of the aerial parts (300 mg/ml) inhibited the

*E. coli* enterotoxin-induced secretory response—which causes a diarrhoeal syndrome—in the rabbit and guinea-pig ileal loop assay (*39, 40*). However, an aqueous extract of the aerial parts was not active (*40*). The constituent diterpene lactones, andrographolide and neoandrographolide, exhibited potent antisecretory activity in vivo against *E. coli* enterotoxin-induced diarrhoea (*40*). Andrographolide (1 mg per loop) was as active as loperamide when tested against heat-labile *E. coli* enterotoxin-induced diarrhoea and more effective than loperamide when tested against heat-stable *E. coli* enterotoxin-induced diarrhoea (*40*). Neoandrographolide (1 mg per loop) was as effective as loperamide when tested against heat-labile *E. coli* enterotoxin-induced diarrhoea and slightly less active than loperamide when tested against heat-stable *E. coli* enterotoxin-induced diarrhoea (*40*). The mechanism of action involves inhibition of the intestinal secretory response induced by heat-labile *E. coli* enterotoxins, which are known to act through the stimulation of adenylate cyclase, and by inhibition of the secretion induced by heat-stable *E. coli* enterotoxins, which act through the activation of guanylate cyclase (*39*). Incubation of murine macrophages with andrographolide (1–50 µmol/l) inhibited bacterial endotoxin-induced nitrite accumulation in a concentration- and time-dependent manner. Western blot analysis demonstrated that andrographolide inhibited the expression of an inducible isoform of nitric oxide synthase linked to endotoxin-induced circulatory shock (*41*).

**Anti-inflammatory activity**

Intragastric administration of deoxyandrographolide, andrographolide, neoandrographolide or 11,12-didehydrodeoxyandrographolide to mice inhibited the increase in cutaneous or peritoneal capillary permeability induced by xylene or acetic acid, and reduced acute exudation in Selye granulocysts treated with croton oil. 11,12-Didehydrodeoxyandrographolide had the most potent anti-inflammatory activity in vivo (*6*).

**Antimalarial activity**

A 50% ethanol extract of the aerial parts inhibited the growth of *Plasmodium berghei* both in vitro (100 mg/ml) and in mice after intragastric administration (1 g/kg body weight) (*42*). Intragastric administration of a 1-butanol, chloroform or ethanol–water extract of the aerial parts to *Mastomys natalensis* inhibited the growth of *P. berghei* at doses of 1–2 g/kg body weight (*43*). Andrographolide (5 mg/kg body weight) and neoandrographolide (2.5 mg/kg body weight) were also effective when administered by gastric lavage (*43*).

**Antivenom activity**

Intraperitoneal injection of an ethanol extract of the aerial parts (25 g/kg body weight) to mice poisoned with cobra venom markedly delayed the occurrence of respiratory failure and death (*6, 44*). The same extract induced contractions in guinea-pig ileum at concentrations of 2 mg/ml. The contractions were

enhanced by physostigmine and blocked by atropine, but were unchanged by antihistamines (*44*). These data suggest that extracts of the aerial parts do not modify the activity of the nicotinic receptors but produce significant muscarinic activity, which accounts for its antivenom effects (*6*, *44*).

### Antihepatotoxic activity

The aerial parts and their constituent andrographolides have antihepatotoxic activity in vitro and in vivo (*45–54*). Intraperitoneal administration of a methanol extract of the aerial parts (861.3 mg/kg body weight) to mice reduced hepatotoxicity induced by carbon tetrachloride ($CCl_4$), and reversed $CCl_4$-induced histopathological changes in the liver (*52*). Intraperitoneal administration of andrographolide (100 mg/kg body weight) to mice inhibited the $CCl_4$-induced increase in the activity of serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, alkaline phosphatase, bilirubin and hepatic triglycerides (*52*). Intraperitoneal administration of a methanol extract of the aerial parts (500 mg/kg body weight) to rats also suppressed the $CCl_4$-induced increase in the activity of serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, alkaline phosphatase and bilirubin (*51*). Intragastric administration of an aqueous extract of the aerial parts (500 mg/kg body weight) to ethanol-treated rats decreased the activity of serum transaminases and suppressed histopathological changes in the liver (*49*). Andrographolide, the major antihepatotoxic component of the plant, exerted a pronounced protective effect in rats against hepatotoxicity induced by $CCl_4$ (*47*), D-galactosamine (*54*), paracetamol (*48*) and ethanol (*49*). Andrographolide was more effective than silymarin, the standard hepatoprotective agent (*47*, *48*).

## *Clinical pharmacology*

### The common cold

Herba Andrographidis has been used clinically for symptomatic treatment of the common cold and uncomplicated sinusitis, pharyngotonsillitis, pneumonia and bronchitis (*6*, *17*, *18*, *20*). A placebo-controlled, double-blind clinical trial assessed the efficacy of a standardized extract of the aerial parts (containing 4% andrographolides) for treatment of the common cold in 61 adult patients. A significant reduction ($P < 0.0001$) in clinical symptoms such as sore throat, tiredness, muscular ache and malaise was observed on day 4 in the group receiving 1200 mg extract daily, as compared with the placebo group. No adverse reactions were reported in either group (*17*).

A randomized, placebo-controlled, double-blind pilot trial was conducted to evaluate the efficacy of a standardized extract of the aerial parts (containing 4% andrographolides) on the initial symptoms of the common cold and uncomplicated sinusitis. Fifty adult patients received either 1020 mg extract or a placebo daily for 5 days. The results demonstrated that patients in the treated group took less sick leave than those in the placebo group (0.21 day compared to 0.96 day). Furthermore, 68% of treated patients felt totally recovered, as

compared with 36% of the placebo group. Also 55% of the treated patients thought that the course of illness was much easier than normal, as compared with 19% of the placebo group (*18*).

A randomized, placebo-controlled, double-blind study evaluated a standardized extract of the aerial parts (containing 4% andrographolides) in the prophylaxis of the common cold in 107 schoolchildren during the winter season. The children received either 200 mg extract or a placebo daily for 3 months and were evaluated weekly by a physician. There was no difference in the occurrence of colds between the two groups during the first 2 months of treatment. However, after the third month of treatment, there was a significant difference ($P < 0.05$) in the occurrence of the common cold in the treated group (30%) as compared with the placebo group (62%) (*19*).

A randomized, double-blind comparison study of 152 adult patients with pharyngotonsillitis evaluated the efficacy of powdered aerial parts (6 g daily) and paracetamol (1 capsule of 325 mg as needed) for improving symptomatology. Baseline evaluation showed no significant difference between the two groups. The crude drug was as effective as paracetamol in reducing the incidence of sore throat and fever after 3 days of treatment (*20*). In a study without controls, treatment of patients with a standardized extract of *A. paniculata* (containing 4% andrographolides) reduced the incidence of fever associated with the common cold. The body temperature of patients treated with the extract was lowered in less than 48 hours after treatment (*55*). This finding was confirmed in a later study (*17*).

### Urinary infections

A clinical trial compared the efficacy of Herba Andrographidis, co-trimoxazole (sulfamethoxazole + trimethoprim) and norfloxacin in the prevention of urinary tract infections after extracorporeal shock wave lithotripsy. Patients received a 5-day course of either Herba Andrographidis (4 tablets of 250 mg, three times daily) or co-trimoxazole (2 tablets of 25 mg, twice daily) or norfloxacin (1 tablet of 200 mg, twice daily). After 1 month of treatment, urinalysis results of 100 patients demonstrated that pyuria, haematuria and proteinuria were reduced in all treatment groups, and there was no significant difference between the three treatments (*21*).

### Dysentery

The aerial parts have been used for the treatment of acute bacillary dysentery and enteritis (*2, 6, 22, 23*). In clinical studies, the combination of andrographolide and neoandrographolide was reported to be more effective than either furazolidine or chloramphenicol in the treatment of bacillary dysentery (*6*). A randomized, double-blind clinical study of 200 patients compared the efficacy of the powdered aerial parts with tetracycline in the treatment of acute diarrhoea and bacillary dysentery (*22, 23*). Patients received capsules of either the aerial parts or tetracycline (both 500 mg, four times daily) for 3 days. Compared with tetracycline, the aerial parts decreased the diarrhoea (both the fre-

quency and amount of discharge) (*22*). Furthermore, the aerial parts were more effective in treating diarrhoea resulting from shigellosis than from cholera (*22*).

### Infectious hepatitis

Administration of a decoction of the aerial parts to patients with infectious hepatitis was reported to provide symptomatic relief (*24*).

## Contraindications

Herba Andrographidis should not be used during pregnancy or lactation. Herba Andrographidis is contraindicated in cases of known allergy to plants of the Acanthaceae family.

## Warnings

Due to potential anaphylactic reactions, crude extracts of Herba Andrographidis should not be injected (*6*, *56*).

## Precautions

### *Drug interactions*

Extracts of Herba Andrographidis may have a synergistic effect with isoniazid (*6*).

### *Carcinogenesis, mutagenesis, impairment of fertility*

Herba Andrographidis extracts are not mutagenic in vitro (*57*) and have anti-mutagenic activity (*58*). A standardized extract of *A. paniculata* did not produce reproductive toxicity in male rats after 60 days of intragastric administration of 20–1000 mg/kg body weight daily (*59*).

### *Pregnancy: teratogenic effects*

See Contraindications.

### *Pregnancy: non-teratogenic effects*

In vivo studies in mice and rabbits suggest that Herba Andrographidis may have abortifacient activity (*6*, *60*). Conversely, no interruption of pregnancy, fetal resorption or decrease in the number of live offspring was observed in pregnant rats after intragastric administration of an extract of the aerial parts at 2 g/kg body weight during the first 9 days of gestation (*61*). Since potential antagonism exists between Herba Andrographidis and endogenous progesterone, Herba Andrographidis should not be used during pregnancy (*2*, *61*).

### *Nursing mothers*

See Contraindications.

### *Other precautions*

No information available on general precautions or precautions concerning drug and laboratory test interactions; or paediatric use. Therefore, Herba Andrographidis should not be administered to children without medical supervision.

## Adverse reactions

Large oral doses of Herba Andrographidis may cause gastric discomfort, vomiting and loss of appetite (*6*). These side-effects appear to be due to the bitter taste of andrographolide (*6*). Anaphylactic reactions may occur if the crude drug extract is injected (*6, 56*). Two cases of urticaria have been reported (*18*).

## Dosage forms

Crude drug, capsules, tablets and pills (*1, 2, 6*). Store in a well-closed container, protected from light and moisture.

## Posology

(Unless otherwise indicated)
For pyrexia: a decoction from 3 g crude drug, twice daily (*1, 5*). For the common cold: 1.5–3.0 g powdered crude drug three times daily, after meals and at bedtime (*1*). For diarrhoea: a decoction from 3–9 g crude drug as a single dose as needed (*1, 5*), or two tablets of 500 mg four times daily, after meals and at bedtime (*5*).

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# Radix Angelicae Sinensis

## Definition

Radix Angelicae Sinensis consists of the dried roots of *Angelica sinensis* (Oliv.) Diels (Apiaceae) (*1*).

## Synonyms

Although *Angelica sinensis* has also been referred to as *Angelica polymorpha* Maxim. var. *sinensis* (the latter being a synonym for *A. polymorpha* Maxim. (*2*)), their synonymy has not yet been firmly established (J.C. Regalado, personal communication, 1999). Apiaceae are also known as Umbelliferae.

## Selected vernacular names

Can qui, Chinese Angelica, dangdanggui, dang gui, dong quai, duong qui handanggui, hashyshat almalak, kara toki, langdu danggui, min-gui, tang-kuei, tangkuei tần q́ui (*1*, *3–6*).

## Geographical distribution

Indigenous to China (*3*, *4*).

## Description

A fragrant, perennial herb, 0.5–1.0 m high. Stem glabrous and purplish, with light, linear striations. Inferior leaves tripinnate; superior leaves often pinnate; segments oval, dentate-incised, teeth obtuse. Petiole 3–11 cm long, sheathed; bracts rudimentary, not prominent. Umbels 10–14, radiate on top of the plant, rays irregular, interior margin uneven; bracteoles, narrow-linear 2–4; pedicels slender; carpophore bipartite; each umbel multiflorous (12–36 flowers); umbel stem 0.3–1.5 cm long. Flowers white, 5 petals, glabrous, incurvate at the tips. Carpels dorsally compressed, square-elliptical, the base cordiform, the tip rounded or lightly notched; dorsal veins 5, closely placed, projecting; central vein barely winged, marginal veins with very large wings; ducts oleaginous, 1 in each sinus, 2 in the commissure (*4*).

## Plant material of interest: dried roots

### *General appearance*

Somewhat cylindrical, 3–5 or more branches at the lower part, 15–25 cm long. Externally yellowish-brown to brown, longitudinally wrinkled and transversely lenticellate. Root stocks 1.5–4 cm in diameter, annulated, apex obtuse, showing purple or yellowish-green remains of stems and leaf sheaths; main roots lumpy on the surface, branching roots 0.3–1.0 cm in diameter, upper portion thick and lower portion thin, mostly twisted, with a few rootlet scars. Texture flexible, fracture yellowish-white or yellowish-brown, thick epidermis, showing some clefts and numerous brown spotted secretory cavities; wood paler in colour than the bark, cambium ring yellowish-brown (*1*).

### *Organoleptic properties*

Odour: strongly aromatic; taste: sweet, pungent, slightly bitter (*1*).

### *Microscopic characteristics*

Cork cells in several layers. Cortex narrow, with a few scattered oil cavities. Phloem cleft, broad (25–160 µm in diameter), relatively large on outer side, gradually becoming smaller, surrounded by 6–9 secretory cells, oil cavities and oil tubes. Cambium in a ring. Xylem rays, 3–5 cells wide; vessels scattered singly or in groups of 2–3, arranged radially; parenchymatous cells contain starch grains (*1*).

### *Powdered plant material*

Yellowish-brown; parenchymatous cells in phloem are fusiform, with slightly thickened walls, very oblique criss-cross striations, thin transverse septa sometimes visible; scalariform and reticulate vessels frequent, up to 80 µm in diameter; fragments of oil cavities sometimes visible (*1*).

## General identity tests

Macroscopic and microscopic examinations (*1*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*7*).

### *Foreign organic matter*

Free of foreign matter (*1*).

### *Total ash*
Not more than 7.0% (*1*).

### *Acid-insoluble ash*
Not more than 2.0% (*1*).

### *Alcohol-soluble extractive*
Not less than 45% using 70% ethanol (*1*).

### *Pesticide residues*
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*8*). For other pesticides, see the *European pharmacopoeia* (*8*), and the WHO guidelines on quality control methods for medicinal plants (*7*) and pesticide residues (*9*).

### *Heavy metals*
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*7*).

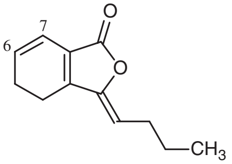
### *Radioactive residues*
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*7*) for the analysis of radioactive isotopes.

### *Other purity tests*
Chemical, water-soluble extractive and loss on drying tests to be established in accordance with national requirements.

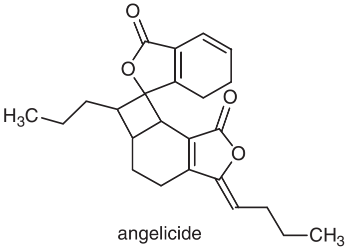
## Chemical assays
Methods for both qualitative and quantitative determination of the alkyl phthalide components by high-performance liquid chromatography have been developed (*10, 11*). National requirements for quantitative criteria should be established with respect to the concentration ranges reported for the essential oil (0.4–0.7%) (*4*) and ligustilide (0.5–5.0%) (*10*).

## Major chemical constituents
The characteristic components are the simple alkyl phthalides (ligustilide, (*Z*)-ligustilide, (*Z*)-6,7-epoxyligustilide, angelicide, (*Z*)-butylidenephthalide, butylphthalide, 2,4-dihydrophthalic anhydride), which are the major components of the essential oil fraction of the roots. Other characteristic components of the oil have been identified as terpenes (β-cadinene, carvacrol and *cis*-β-ocimene). The non-volatile constituents reported are phenylpropanoids ((*E*)-ferulic acid,

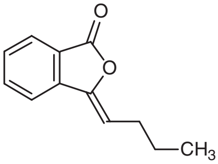
coniferyl ferulate); benzenoids (valerophenone-*o*-carboxylic acid and vanillic acid); and coumarins (angelol G, angelicone and umbelliferone) (*3, 4, 10, 11*). It has been shown by high-performance liquid chromatography that the major chemical constituent of the roots is ligustilide, which can account for over 5% (*10*). Polysaccharide fractions of low relative molecular mass have also been reported (*12, 13*). The structures of the characteristic constituents are presented below.



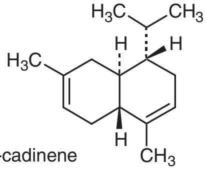

(*Z*)-ligustilide



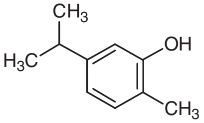

angelicide



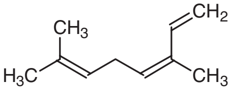

(*Z*)-butylidenephthalide
((*Z*)-ligusticum lactone)



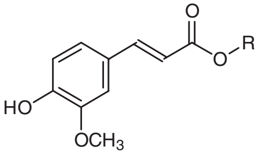

β-cadinene



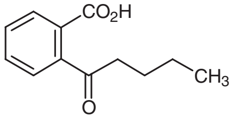

carvacrol



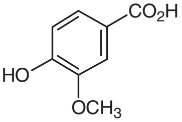

*cis*-β-ocimene



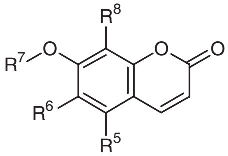

(*E*)-ferulic acid R = H
coniferyl ferulate R = Con



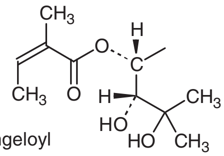

valerophenone-*o*-carboxylic acid
(ligusticumic acid)



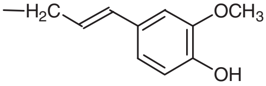

vanillic acid



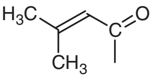

| | $R^5$ | $R^6$ | $R^7$ | $R^8$ |
|---|---|---|---|---|
| umbelliferone | H | H | H | H |
| angelicone | $OCH_3$ | H | $CH_3$ | Sen |
| angelol G | H | Ang | $CH_3$ | H |




Ang = angeloyl




Con = (*E*)-coniferyl




Sen = senecioyl

## Medicinal uses

### *Uses supported by clinical data*

None. Although Radix Angelicae Sinensis has been alleged to be useful for the treatment of menopausal symptoms, a randomized, placebo-controlled clinical trial concluded that 4.5 g of the root daily for 24 weeks did not alleviate menopausal symptoms, such as hot flushes (*14*).

### *Uses described in pharmacopoeias and in traditional systems of medicine*

Treatment of menstrual disorders such as irregular menstruation, amenorrhoea and dysmenorrhoea (*1, 3, 15–19*). As an analgesic for symptomatic treatment of rheumatic arthralgia, abdominal pain and in the management of post-operative pain (*1, 20*). Treatment of constipation (*1*), anaemia (*1, 20*), chronic hepatitis and cirrhosis of the liver (*20*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of dehydration, lumbago, abnormal menstruation, menopausal symptoms (including hot flushes), hypertonia and nervous disorders (*18, 21*).

## Pharmacology

### *Experimental pharmacology*

#### Smooth muscle contraction

Hot aqueous extracts of Radix Angelicae Sinensis stimulated smooth muscle contractions of the bladder, intestine and uterus when administered intravenously to dogs (10 g/kg body weight) (*22*). Intravenous administration of an aqueous or 95% ethanol extract of the roots to cats, rats and rabbits increased the strength of the contractions and tone of uterine smooth muscles (*4*). In vitro assays demonstrated that a decoction of the roots stimulated the $H_1$ receptor of mouse uterus (*23*). The active constituent responsible for this activity is an aqueous- and alcohol-soluble, non-volatile component, the structure of which is unknown (*4*). Conversely, ligustilide, a constituent of the essential oil of the roots, inhibited contractions of isolated uteri from various animal models (*20, 24*). Intraperitoneal administration of ligustilide (0.14 ml/kg body weight) to guinea-pigs inhibited asthmatic reactions induced by acetylcholine and histamine (*25*). Ligustilide (32.5–130.0 µl/ml) inhibited smooth muscle contractions induced by barium sulfate, acetylcholine and histamine in isolated guinea-pig trachea (*25*).

#### Antihepatotoxic activity

Intraperitoneal administration of a decoction of the roots (11 ml/kg body weight) ameliorated galactosamine-induced hepatotoxicity in rats (*26*). Ferulic

acid, a constituent of the roots, protected rat liver mitochondria against damage induced by oxygen free radicals (*27*). Intragastric pretreatment of mice with sodium ferulate (100 mg/kg body weight) daily for 10 days alleviated liver toxicity induced by paracetamol (*28*) and prednisolone (*29*), and bromobenzene-induced liver injury (*30*).

### Cardiovascular activity

Cardiac haemodynamic studies demonstrated that intravenous administration of an aqueous root extract (2 g/kg body weight) to anaesthetized dogs increased coronary blood flow from 88 ml before administration to 128 ml (per 100 g cardiac muscle/minute post-injection). Coronary vascular resistance and myocardial oxygen consumption also decreased, while the heart rate decreased or remained unchanged (*31*). An extract of the roots increased coronary blood flow in isolated guinea-pig hearts (*32*).

In animal models, both aqueous and ethanol extracts of the roots had an effect on arrhythmias induced by epinephrine, barium chloride and digitalis (*32, 33*). Intravenous administration of an ethanol extract of the roots (4 g/kg body weight) antagonized chloroform- and epinephrine-induced arrhythmias in cats (*34*). Ethanol extracts of the roots and ferulic acid restored normal sinus rhythm after ouabain-induced arrhythmia in isolated ventricular muscle from cats (*20*). Aqueous extracts of the roots reduced the action potential amplitude and maximal upstroke velocity of the Q phase, and prolonged the effective refractory period and the duration of the action potential in guinea-pig myocardium (*35*). Intravenous administration of an aqueous extract of the roots (50 mg/kg body weight) to rabbits with ligation of the left anterior descending coronary artery provided protection against ischaemia- and reperfusion-induced myocardial dysfunction and injury (*36*). An aqueous extract of the roots bound to nitrendipine and diltiazem receptors, thereby demonstrating calcium channel blocking activity (*37*). A ligustilide dimer, isolated from the roots, inhibited [$^3$H]nitrendipine binding to dihydropyridine-sensitive calcium channels (inhibitory concentration of 50% [$IC_{50}$] 0.4 μmol/l) (*38*). Since calcium channel blockers are known to have pronounced effects on the cardiovascular system, this activity may explain some of the reported effects of root extracts on the cardiovascular system.

### Antithrombotic activity

In vitro and in vivo studies have shown that extracts of the roots inhibit platelet aggregation and have antithrombotic activity (*20*). Aqueous extracts of the roots (200 mg/ml) or ferulic acid (0.4 mg/ml) inhibited platelet aggregation induced by ADP or collagen in vitro (*39*). A hot aqueous extract of the roots (500 mg/ml) or ferulic acid (1 mg/ml) inhibited thrombin-induced platelet aggregation and release of [$^3$H]5-hydroxytryptamine from labelled platelets in vitro (*39*). An aqueous extract of the roots inhibited both ADP- and collagen-induced platelet aggregation when administered intravenously to rats (200 mg/ml) (*20, 39*). The mechanism of action appears to be via inhibition of cyclooxygenase and throm-

boxane $A_2$ synthase by ferulic acid, leading to decreased production of thromboxane $A_2$ (*40*). The antithrombotic activity of the drug is associated with inhibition of platelet aggregation, reduction in the concentration of plasma fibrinogen, changes in cell surface charge and a decrease in blood viscosity (*20*).

Intraperitoneal administration of polysaccharides isolated from the roots increased haematopoiesis in mouse bone marrow, as determined by an increase in colony-forming units in the marrow cells (*12, 41*). The polysaccharides promoted the proliferation and differentiation of haematopoietic progenitor cells in healthy and anaemic mice (*13*). Results of this study indicated that the polysaccharides may enhance haematopoiesis by stimulating macrophages, fibroblasts and lymphocytes in haematopoietic and muscle tissue to secrete haematopoietic growth factor (*13*).

### *Clinical pharmacology*

#### Menstrual disorders

Although there are a number of case reports concerning the clinical use of Radix Angelicae Sinensis in the treatment of amenorrhoea and dysmenorrhoea, these studies were published between 1899 and 1910 (*15–18*). Randomized, controlled clinical trials are needed to confirm these observations. In these early case studies, female patients were treated with 5 ml of a fluidextract of the roots three times daily before meals for 1 week before menstruation. The treatment relieved premenstrual pain and induced menstrual flow in most cases. No abortifacient activity was observed in two pregnant women treated with the same fluidextract (*15*). In other studies, the fluidextract was used for the treatment of dysmenorrhoea in nulliparous women, and of severe bleeding in multiparous women. Administration of 5 ml of the fluidextract three times daily for 1 week before menstruation was effective in decreasing menstrual pain and chronic endometritis (*16*). Successful treatment of amenorrhoea and dysmenorrhoea in female patients was further reported after administration of the same fluidextract (5 ml, three times daily) (*17, 18*). In another report, 112 women with dysmenorrhoea were treated for 3–7 days with ligustilide dimer isolated from the roots. The efficacy rate was 77%. Minor side-effects were nausea and dizziness, which disappeared after the treatment stopped (*42*).

#### Smooth muscle contraction

Decoctions of the roots reportedly stimulated uterine smooth muscle in female patients, but the doses used and the conditions being treated were not stated (*19*). A decoction of the roots lowered whole blood viscosity after administration to six patients (*11*).

## Contraindications

Radix Angelicae Sinensis should not be administered to children or patients with diarrhoea, haemorrhagic diseases or hypermenorrhoea, and should not be used during pregnancy or lactation (*4*).

## Warnings

No information available.

## Precautions

### Drug interactions

Decreased prothrombin times were reported in rabbits that received both a single subcutaneous dose of warfarin (2 mg/kg body weight) and a repeated oral dose of Radix Angelicae Sinensis (2 g/kg body weight twice daily for 3 days) (*43*). Therefore, patients receiving anticoagulant therapy should be advised against taking Radix Angelicae Sinensis without medical supervision.

### Pregnancy: teratogenic effects

See Contraindications.

### Pregnancy: non-teratogenic effects

See Contraindications.

### Nursing mothers

See Contraindications.

### Paediatric use

See Contraindications.

### Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions; or carcinogenesis, mutagenesis and impairment of fertility.

## Adverse reactions

Oral administration of Radix Angelicae Sinensis is generally regarded as having few side-effects; however, headaches may occur in sensitive individuals (*14*, *19*). No adverse reactions were reported in 40 people who received an aqueous root extract by intravenous administration (240 ml/person) for 30 days (*19*).

## Dosage forms

Powdered crude drug and fluidextracts (*4*). Store in an airtight container in a cool, dry place protected from moisture (*1*).

## Posology

(Unless otherwise indicated)
Daily dosage: 4.5–9 g crude drug (*1*).

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# Flos Calendulae

## Definition

Flos Calendulae consists of the dried ligulate florets or composite flowers of *Calendula officinalis* L. (Asteraceae) (*1–3*).

## Synonyms

Asteraceae are also known as Compositae.

## Selected vernacular names

Atunjaq, calendula, Chinese safflower, cuc kim tiên, djamir, djomaira, feminell, flamenquilla, fleur de calandule, fleur de souci, fleur de souci officinal, fleurs de tous les mois, garden marigold, gold-bloom, Goldblume, gole hamisheh bahar, hen and chickens, Körömvirag, lellousha, maravilla, marigold, mary-bud, ok-hhawan, pot marigold, qaraqus, qawqhan, quaqahan, ringflower, Ringelblüten, saialill, sciure'e Sant'antonio, souci, souci des jardins, tabsoult, toukinsenka, tousslat, uchu k'aspa, virreina, xu xi, zergul zerzira, zobeida, zubaydah (*4–7*).

## Geographical distribution

Indigenous to central, eastern and southern Europe. Cultivated commercially in North America, the Balkans, Eastern Europe and Germany (*6*, *8*).

## Description

An annual herb, much branched from the base, very aromatic, up to 0.3–0.6 m high; stem angular, hairy and solid. Leaves sessile, light green, with semi-amplexicaul base; entire, undulate or remotely denticulate; glandular hairs on both surfaces; lower leaves spatulate, obtuse, sometimes acute at the apex, 10–20 cm long and 1–4 cm wide; higher leaves oblong and mucronate, 4–7 cm long. Involucral bracts 7–15 mm long, covered with long, glandular hairs; inner involucral bracts with pellucid, scarious margin; marginal flowers in cultivated plants often multi-seriate; corolla oblong-spatulate, bright yellow or orange, 15–25 mm long and 3 mm wide, 1–3-toothed with 4 or 5 veins, marginally entire, covered at the base with patent, long, thick hairs; corolla of disc flowers rounded, 3-dentate top, 1.5–2.5 cm long and 4–7 mm in diameter, 5 mm long

tube and moderately widened limb. Stigma short, thick, hairy; ovary oblong, 0.5 mm in length, pubescent, shrivelling after anthesis. Achenes narrowly oblong, strongly curved, faintly ribbed, thinly pubescent or glabrous, 10–12 mm long, outer achenes warty-ribbed outside, inner achenes prickly-warty, often with broad, thick margins (*2, 7, 9*).

## Plant material of interest: dried ligulate florets and composite flowers

### *General appearance*

Ligulate florets consist of a yellow, orange or orange-yellow ligule, 3–5 mm wide and about 7 mm in the middle part, with 3-toothed apex and hairy, partly sickle-shaped, yellowish-brown to orange-brown tube with projecting style and 2-lobed stigma; occasionally with a partly bent yellowish-brown to orange-brown ovary. Tubular florets about 5 mm long, consist of yellow, orange-red or red-violet 5-lobed corolla and yellowish-brown or orange-brown tube, hairy in its lower part, mostly with a bent yellowish-brown to orange-brown ovary (*1*).

### *Organoleptic properties*

Odour: faint, pleasantly aromatic (*10, 11*); taste: bitter (*2*).

### *Microscopic characteristics*

Inner epidermal cells of ray floret elongated, rectangular and almost straight-walled, cuticle faintly striated; stomata absent; outer epidermal cells similar, but with 3 or 4 anomocytic stomata; trichomes very numerous on the tube, biseriate; stigma epidermal cells straight-walled, polygonal. In disc floret, outer epidermal cells elongated, straight or slightly sinuous-walled, stomata absent; abundant trichomes on area below point of insertion of the stamens, mainly glandular, uniseriate or biseriate. Within the upper part of the anthers, a layer of isodiametric to elongated, moderately thick-walled, lignified and pitted cells; pollen grains spherical, up to 45 µm in diameter, with 3 germinal pores, exine finely granular with numerous short spines; apex of stigma covered by short, bulbous papillae (*2*).

### *Powdered plant material*

Yellow-green; fragments of corollas containing light yellow oil droplets; some corollas with fairly large anomocytic stomata, others containing prismatic and very small clusters of calcium oxalate crystals. Covering trichomes biseriate, multicellular and conical; glandular trichomes with a uniseriate or biseriate, multicellular stalk and a large, ovoid, biseriate, multicellular head. Spherical

pollen grains up to 45 µm in diameter, exine finely granular with numerous short spines and with 3 germinal pores; occasional fragments of stigmas with short, bulbous papillae (*1*).

## General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for flavonoid content (*1*, *2*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

### *Foreign organic matter*

Not more than 5% bracts and not more than 2% other foreign matter (*1*, *2*).

### *Total ash*

Not more than 10% (*1*, *2*).

### *Acid-insoluble ash*

Not more than 2% (*2*).

### *Water-soluble extractive*

Not less than 20% (*2*).

### *Loss on drying*

Not more than 10% (*1*).

### *Pesticide residues*

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

### *Heavy metals*

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

### *Radioactive residues*

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

### *Other purity tests*

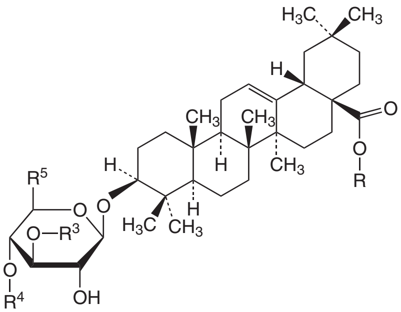
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

## Chemical assays

Contains not less than 0.4% flavonoids, calculated as hyperoside, by spectrophotometry (*1*). A high-performance liquid chromatography method is also available (*15*).

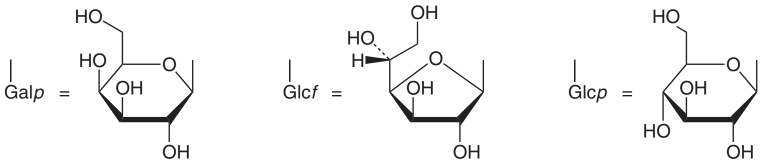
## Major chemical constituents

The major constituents are triterpene saponins (2–10%) based on oleanolic acid (i.e. calendulosides) and flavonoids (3-*O*-glycosides of isorhamnetin and quercetin), including astragalin, hyperoside, isoquercitrin and rutin. Other constituents include essential oil, sesquiterpenes (e.g. caryophyllene) and triterpenes (e.g. α- and β-amyrins, lupeol and lupenone) (*5*, *6*, *16*). Polysaccharides have also been reported (*17*). The structures of the characteristic triterpene saponins and flavonoids are presented below.

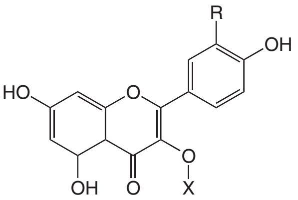



calendulosides

| | R | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|
| A | H | H | Gal*p* | $CH_2OH$ |
| E | H | H | H | $CO_2H$ |
| F | Glc*p* | H | H | $CO_2H$ |
| H | Glc*p* | Gal*p* | H | $CO_2H$ |

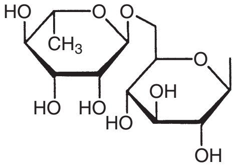



β-D-galactopyranosyl β-D-glucofuranosyl β-D-glucopyranosyl



| | R | X |
|---|---|---|
| astragalin | H | Glc*p* |
| hyperoside | OH | Gal*p* |
| isoquercitrin | OH | Glc*f* |
| rutin | OH | Rha*p*-(1 → 6)-Glc*p* |

Rha*p*-(1 → 6)-Glc*p* =



*O*-6-deoxy-α-L-mannopyranosyl-(1 → 6)-β-D-glucopyranosyl

# Medicinal uses

## *Uses supported by clinical data*

None.

## *Uses described in pharmacopoeias and in traditional systems of medicine*

External treatment of superficial cuts, minor inflammations of the skin and oral mucosa, wounds and ulcus cruris (*2*, *18*, *19*).

## *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of amenorrhoea, angina, fevers, gastritis, hypotension, jaundice, rheumatism and vomiting (*2*, *5*, *6*).

# Pharmacology

## *Experimental pharmacology*

### Phagocytosis

Three polysaccharides isolated from an aqueous extract of Flos Calendulae enhanced phagocytosis in human granulocytes in vitro in the colloidal carbon clearance test (*17*). Intraperitoneal injection of a polysaccharide fraction isolated from an aqueous extract of the flowers to mice (10 mg/kg body weight) enhanced phagocytosis (*20*). Intraperitoneal administration of an unsaponifiable fraction (0.5 ml) of a hydroalcoholic extract of the flowers weakly stimulated phagocytosis in mice inoculated with *Escherichia coli*. However, the hydroalcoholic extract was not active (*21*).

**Antimicrobial activity**

The essential oil of the flowers inhibited the growth in vitro of *Bacillus subtilis, Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Candida albicans* (*22*). A flavonoid fraction isolated from the flowers inhibited the growth in vitro of *S. aureus, Sarcina lutea, E. coli, Klebsiella pneumoniae* and *Candida monosa* (*23*). However, chloroform, ethanol, methanol or water extracts of the flowers did not inhibit bacterial growth in vitro (*24–26*). Acetone, ethanol or water extracts inhibited the growth in vitro of the fungus *Neurospora crassa* (*27*). Extracts of the flowers inhibited the growth in vitro of *Trichomonas vaginalis* (*28*). Oxygenated terpenes appear to be responsible for the antimicrobial activity (*29*).

**Antiviral activity**

A tincture of the flowers suppressed the replication of herpes simplex, influenza A2 and influenza APR-8 viruses in vitro (*30*). However, an aqueous extract of the flowers was not active (*31*). A chloroform extract of the flowers inhibited the replication of HIV-1 in acutely infected lymphocytic MOLT-4 cells in vitro ($IC_{50}$ 0.4 mg/ml) (*32*). A chloroform extract also inhibited HIV-1 reverse transcriptase activity in a dose-dependent manner ($ED_{50}$ 51.0 μg/ml) (*32*). A 5% hot aqueous extract of the flowers (2 ml) inhibited the replication of encephalitis virus after intraperitoneal administration to mice (*33*).

**Anti-inflammatory activity**

Topical application of a 70% ethanol extract of the flowers to mice at a dose of 1.2 mg/ear (corresponding to 4.16 mg crude drug) reduced croton oil-induced ear oedema by 20% (*34*). External application of a carbon dioxide extract of the flowers (300 μg/cm$^2$) suppressed croton oil-induced ear oedema in mice (*34*). The triterpene fraction of an extract of the flowers had marked anti-inflammatory activity in mice (1 μg/ear) against ear oedema induced by 12-*O*-tetradecanoylphorbol-13-acetate (*35*). Faradiol esters isolated from the flowers (240 μg/cm$^2$) inhibited croton oil-induced ear oedema in mice (*36*). Intragastric administration of an aqueous extract of the flowers (100 mg/kg body weight) inhibited carrageenan-induced footpad oedema in rats (*37*). However, an 80% ethanol extract of the flowers was weakly active (11% inhibition) at a concentration of 100 mg/kg body weight administered orally 1 hour prior to induction of oedema (*38*). Isorhamnetin glycosides isolated from the flowers inhibited rat lung lipoxygenase in vitro (*39*).

**Wound-healing activity**

External application of a hydroalcoholic extract accelerated the rate of contraction and epithelialization of excision wounds in rats (*40*). A 3% freeze-dried aqueous extract of the flowers induced vascularization in the chick chorioallantoic membrane assay. Histological sections of the treated chorioallantoic

membranes also indicated the presence of hyaluronan, a tissue glycosaminoglycan associated with neovascularization (*41*).

### *Clinical pharmacology*

Although no randomized, controlled clinical trials have been performed, two case reports in the early medical literature support the traditional use of Flos Calendulae. The reports describe the use of a strong tincture of the flowers applied on compresses to reduce inflammation and suppuration, and to accelerate the healing of wounds (*42*, *43*). These reports may be of historical value only.

## Contraindications

Flos Calendulae is contraindicated in cases of known allergy to plants of the Asteraceae (Compositae) family (*18*).

## Warnings

No information available.

## Precautions

### *Carcinogenesis, mutagenesis, impairment of fertility*

Saponins isolated from Flos Calendulae were not mutagenic at a concentration of 400 μg/ml in the *Salmonella*/microsome assay using *S. typhimurium* strain TA98, with or without S9 metabolic activation (*44*). Extracts of the flowers were not carcinogenic after daily intragastric administration of 0.15 g/kg body weight to rats (for 22 months) or hamsters (for 18 months) (*45*). Mutagenicity testing of the fluidextract in the *Salmonella*/microsome assay (using *S. typhimurium* strains TA98, TA100, TA1535 and TA1537) was negative at concentrations of up to 5 mg/plate. The mouse bone marrow micronucleus test was also negative after daily administration of up to 1 g/kg body weight for 2 days (*46*). A fluidextract of the flowers (100 mg/ml, 60% ethanol) was genotoxic in both mitotic crossing-over and chromosome segregation when assayed for mitotic segregation in the heterozygous diploid D-30 of *Aspergillus nidulans* (*46*).

### *Other precautions*

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Flos Calendulae should not be administered during pregnancy or lactation or to children without medical supervision.

## Adverse reactions

Weak skin-sensitization has been reported (*47*).

## Dosage forms

Infusion for topical use; aqueous and alcohol extracts, tinctures and ointment for external use (*2*, *18*, *19*). Store in a well-closed container, protected from light (*1*).

## Posology

(Unless otherwise indicated)

Topical application: an infusion of 1–2 g/150 ml (*18*). External use: a 40% alcohol extract (1 : 1), or tincture (1 : 5) in 90% alcohol (*2*). For the treatment of wounds, the tincture is applied undiluted; for compresses, the tincture is usually diluted at least 1 : 3 with sterile water (*18*, *48*, *49*). Ointment: 2–5% (*48*, *50*).

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# Flos Caryophylli

## Definition

Flos Caryophylli consists of the dried flower buds of *Syzygium aromaticum* (L.) Merrill et L.M. Perry (Myrtaceae) (*1–5*).

## Synonyms

*Caryophyllus aromaticus* L., *Eugenia aromatica* (L.) Baill., *E. caryophylla* Thunb., *E. caryophyllus* (C. Spreng.) Bull. et Harr., *Jambosa caryophyllus* (Spreng.) Nied., *Myrtus caryophyllus* Spreng. (*1*, *5–8*).

## Selected vernacular names

Benefundi, choji, choko, chouji, choukou, clavero, clavo de olor, clous de girofle, clove, cloves, colve, ding huong, dingxiang, flores caryophylli, Gewürznelken, girofle, giroflier, glove, gurunful, harilik negipuu, kaan phluu, kaan pluu, kade, kanumfari, karafwu, karanho, kau-phlu, konofuru, koronfol, lauang, laung, lawang, Nägelein, osaragbogo-eze, qaranfal, qoranful, qronfel, szegfüszeg, ud-nuwwar (*1*, *6–9*).

## Geographical distribution

Indigenous to the Moluccas and southern Philippines, but currently cultivated in many tropical areas including Africa (e.g. Madagascar and United Republic of Tanzania), South America, Indonesia, Malaysia and Sri Lanka (*7,8*).

## Description

Small evergreen trees, 10–20 m high. Leaves opposite, petiolate, lanceolate, pinkish to dark green, with translucent, aromatic glands, have a pungent odour when young. Inflorescence occurs as racemose panicles and bears buds that take on the form of nails before blossoming. Flowers red with 4 concave, overlapping petals that drop off as soon as the flower opens; stamens numerous; 4 calyx lobes. Fruit dark red, fleshy drupe. Buds readily exude oil when pressed or scratched with a fingernail (*7*).

## Plant material of interest: dried flower buds

### General appearance

Flower bud 10–20 mm long, bright reddish-brown to dark brown; lower part (the hypanthium) solid, cylindrical, somewhat flattened, 4-sided, tapering towards the base and bearing at the apex 4 thick, triangular, divergent sepals, alternating with 4 rounded, fragile, unexpanded, membranous, imbricated petals forming a pale, nearly spherical head that encloses numerous stamens, curved inward and inserted on a small disc, and a stiff, slender, erect, single style arising from a depression in the centre. Externally wrinkled; internally, hypanthium contains in its upper portion a 2-celled inferior ovary with numerous ovules attached to the axile placenta; has very large outer zone with numerous shining, oval oil glands near the periphery, numerous vascular bundles in the centre and a dark, lacunose layer abutting on the central zone and columella (*1*).

### Organoleptic properties

Odour: characteristic, strongly aromatic; taste: pungent, spicy, followed by slight numbness (*1*, *3*, *5*).

### Microscopic characteristics

Hypanthium epidermis of small, thick-walled isodiametric cells with very thick cuticle, with stomata with no special subsidiary cells. Parenchymatous layer containing numerous large (up to about 200 µm long), oval, radially elongated, schizo-lysigenous oil glands, arranged in 2 or 3 more or less intermixed layers. Layer of parenchyma and collenchyma containing clusters of calcium oxalate crystals, and traversed by small, irregularly arranged vascular bundles consisting of delicate, spiral vessels (up to 20 µm in diameter), usually accompanied by isolated fusiform, pericyclic fibres (200–650 µm long and up to 40 µm in diameter), having strongly thickened lignified walls. Lacunous layer formed of thin-walled parenchyma. The columella consists of a parenchymatous strand with numerous closely arranged, small vascular bundles. Sepals, with epidermis resembling that of hypanthium and having numerous stomata on outer surface; mesophyll with rounded or stellate cells, numerous ovoid oil glands and clusters of calcium oxalate crystals, and traversed by a few slender vascular bundles. Petals, with epidermis formed of cells with straight, thin walls; stomata, absent; mesophyll, undifferentiated, containing oil glands and cells with clusters of calcium oxalate crystals, and traversed by small vascular bundles. Stamens, with filaments having a central vascular strand and oil glands beneath the epidermis; connective tissue, with a large oil gland in the apex of anther walls, with fibrous layer and minute clusters of calcium oxalate crystals along the line of dehiscence. Pollen grains, triangular, tricolpate, 10–20 µm in diameter. Style, with epidermis similar to that of hypanthium, and consisting of small collenchyma cells, with clusters of calcium oxalate crystals, radially elongated oil glands, and traversed by 2 narrow vascular strands (*1*).

### *Powdered plant material*

Dark brown; abundant fragments of collenchyma and parenchyma with clusters of calcium oxalate crystals, fragments of epidermis with thick-walled cells and few stomata; fragments of vascular or parenchyma tissue showing broken or entire oil glands; numerous fragments of vascular bundles with delicate spiral vessels, ranging from 6 to 45 μm in diameter, mostly 6–10 μm; occasional fusiform, rather thick-walled fibres, 4–20 μm wide; numerous pollen grains, appearing either as equilateral triangular, with truncated, emarginate apices, or oval in outline, 10–20 μm in diameter; fragments of the fibrous layer of anther wall; clusters of calcium oxalate crystals, 10–15 μm in diameter (*1*, *5*).

## General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for the presence of eugenol and β-caryophyllene (*1*, *3–5*, *10*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*11*).

### *Foreign organic matter*

Not more than 4% open buds, peduncles and fruits; not more than 2% deteriorated buds; not more than 0.5% other foreign matter (*5*).

### *Total ash*

Not more than 7% (*4*, *5*).

### *Acid-insoluble ash*

Not more than 0.5% (*4*).

### *Sulfated ash*

Not more than 8% (*12*).

### *Loss on drying*

Not more than 12% (*3*).

### *Pesticide residues*

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*5*). For other pesticides, see the *European pharmacopoeia* (*5*), and the

WHO guidelines on quality control methods for medicinal plants (*11*) and pesticide residues (*13*).

### *Heavy metals*

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*11*).

### *Radioactive residues*

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*11*) for the analysis of radioactive isotopes.

### *Other purity tests*

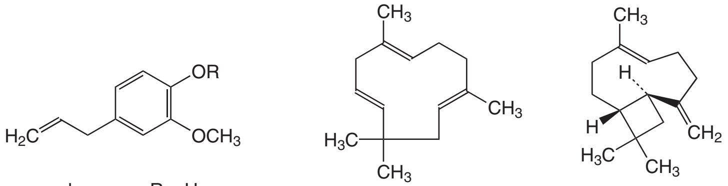
Chemical, water-soluble extractive and alcohol extractive tests to be established in accordance with national requirements.

## Chemical assays

Contains not less than 15% (v/w) essential oil (*1*, *12*), determined by distillation (*5*).

## Major chemical constituents

The major constituent (up to 20%) is an essential oil, which is characterized by the presence of eugenol (60–95%), eugenol acetate (2–27%), and α- and β-caryophyllene (5–10%) (*6*, *8*, *9*, *14*, *15*). The structures of the major constituents are presented below.




eugenol R = H
eugenol acetate R = CO-$CH_3$

α-caryophyllene

β-caryophyllene

## Medicinal uses

### *Uses supported by clinical data*

None.

### *Uses described in pharmacopoeias and in traditional systems of medicine*

External or local applications for the treatment of toothache, and minor infections of the mouth and skin (*7*, *14*, *16*). Also used as an antiseptic for dressing

of minor wounds, and, in the form of lozenges, for sore throats and coughs associated with the common cold (*7*). The essential oil (1–5%) is used in mouthwashes (*16*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of asthma, bleeding gums, dyspepsia, fevers and morning sickness (*9*).

## Pharmacology

### *Experimental pharmacology*

#### Antimicrobial activity

Ethanol (95%) or aqueous extracts of Flos Caryophylli inhibited the growth in vitro of *Staphylococcus aureus* (*17*). The juice of the flower bud inhibited the growth in vitro of *Mycobacterium tuberculosis* (minimal inhibitory concentration [MIC] 1:160) (*18*). The powdered crude drug inhibited the growth in vitro of *Yersinia enterolitica* when added to the medium at a concentration of 1–3% (w/w) (*19, 20*). An aqueous extract of the flower buds inhibited the growth in vitro of *Bacillus subtilis* (*21*). A chloroform extract of the flower buds inhibited the growth in vitro of *Cladosporium werneckii* (*22*). A 50% ethanol extract of the flower buds inhibited the growth of *Aspergillus fumigatus*, *Aspergillus niger*, *Botrytis cinerea*, *Fusarium oxysporum*, *Penicillium digitatum*, *Rhizopus nigricans*, *Trichophyton mentagrophytes*, *Candida albicans* and *Saccharomyces pastorianus* at a concentration of 500 mg/ml (*23*).

Eugenol, one of the active constituents of the flower buds, inhibited the growth in vitro of *Staphylococcus aureus*, *Propionibacterium acnes* and *Pseudomonas aeruginosa*, with an MIC of 0.05, 0.05 and 0.80 mg/ml, respectively (*24, 25*). In other studies, eugenol had a broad spectrum of antibacterial activity in vitro, inhibiting the growth of *Clostridium sporogenes*, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella pullorum*, *Staphylococcus aureus*, *Streptococcus faecalis* and *Comamonas terrigena* at various concentrations (*26, 27*). Eugenol also had a broad spectrum of antifungal activity in vitro, inhibiting the growth of *Alternaria alternata*, *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus*, *Cladosporium werneckii*, *Cladosporium cucumerinum*, *Colletotrichum capsici*, *Helminthosporium oryzae*, *Microsporum canis*, *Penicillium expansum*, *Phytophthora parasitica*, *Rhizopus nodosus*, *Trichophyton mentagrophytes* and *T. rubum* at various concentrations (*27–30*).

#### Antiviral activity

An aqueous extract of the flower buds suppressed the replication of herpes simplex virus (HSV) in vitro at a concentration of 50 µg/ml (*31*). An aqueous extract of the flower buds had antiviral activity against HSV-1 in vitro ($IC_{50}$ 60 µg/ml), and in mice (250 mg/kg body weight by gastric lavage) (*32*). A hot

aqueous extract of the flower buds suppressed the replication of HSV-1, measles virus and poliovirus-1 in Vero cells in vitro at a concentration of 0.5 mg/ml (*33*). Intragastric administration of a decoction of the flower buds (750 mg/kg body weight) decreased HSV-1 genome titres and the severity of HSV infection in mice with recurring herpetic lesions induced by ultraviolet light (*34*). Eugenol at a concentration of 0.1–10 µg/ml demonstrated antiviral activity against HSV and adenovirus-6 in vitro (*35*). Eugeniin isolated from the flower buds exhibited anti-HSV-1 activity in mice (*36*).

### Anti-inflammatory activity

Topical application of a methanol extract of the flower buds (2 mg/ear) suppressed ear oedema in mice induced by 12-*O*-tetradecanoylphorbol-13-acetate (*37*). A methanol extract of the flower buds inhibited interleukin-8 production induced by lipopolysaccharide in rat macrophages in vitro at a concentration of 0.1 mg/ml (*38*). Administration of eugenol (100 mg/kg body weight by gastric lavage or 50 mg/kg body weight intraperitoneally) inhibited carageenan-induced footpad oedema in rats (*39–41*). Intragastric administration of eugenol to rats (33 mg/kg body weight) suppressed footpad and knee oedema induced by *Mycobacterium tuberculosis* (*42*). Administration of eugenol to rats (50 mg/kg body weight intraperitoneally or 100 mg/kg body weight by gastric lavage) inhibited carrageenan-induced footpad oedema (*39, 41*). Topical application of eugenol to mice and rats at a dose of 0.2–2.0 mg/ear suppressed ear oedema induced by 12-*O*-tetradecanoylphorbol-13-acetate and ethyl phenylpropiolate (*43–45*). Topical application of eugenol inhibited carrageenan-induced footpad oedema in rats and reversed passive Arthus reaction in rabbits (*46*). Eugenol inhibited the activities of cyclooxygenase ($IC_{50}$ 12–82 µmol/l) and lipoxygenase ($IC_{50}$ 20–100 µmol/l) in vitro (*41, 46–48*). Eugenol also inhibited the biosynthesis of prostaglandin and thromboxane in various biological systems (*27, 44, 49–51*) and both eugenol and isoeugenol inhibited platelet aggregation ($IC_{50}$ 1.8 µmol/l) (*46*).

### Antioxidant activity

A petroleum ether or ethylene chloride extract of the flower buds exhibited strong antioxidant activity in vitro at a concentration of 0.1% (*52, 53*). A methanol extract of the flower buds inhibited lipid peroxidation induced by carbon tetrachloride, ADP plus arachidonic acid, and ADP plus NADPH ($IC_{50}$ 1.7, 2.6 and 6.4 µg/ml, respectively) (*54*). The antioxidant activity of eugenol has been demonstrated in a wide range of in vitro systems (*55–59*).

### Miscellaneous activities

The essential oil had spasmolytic activity in vitro on isolated guinea-pig trachea and intestine (*60, 61*). Eugenol and caryophyllene had a narcotic effect after intravenous administration of high doses (200–400 mg/kg body weight) (*27, 62*), and a sedative effect after intragastric administration of low doses (1–100 mg/kg body weight) to mice (*60*).

### *Clinical pharmacology*

None.

## Contraindications

Flos Caryophylli is contraindicated in cases of known allergy to plants of the Myrtaceae family.

## Warnings

No information available.

## Precautions

### *Carcinogenesis, mutagenesis, impairment of fertility*

An aqueous or chloroform–methanol extract of the crude drug was not mutagenic in the *Salmonella*/microsome assay at concentrations up to 100 mg/ml (*63*, *64*). A hot aqueous extract was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 or TA100 at a concentration of 50 mg/disk (*63*, *65*). However, a 95% ethanol extract was mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strain TA102 at a concentration of 10 mg/plate (*66*). Eugenol was not mutagenic in vitro (*Salmonella*/microsome assay; up to 600 μg/plate) or in vivo (in mice; 200 mg/kg body weight, by intramuscular injection) (*67–69*). Local application of eugenol reduced the carcinogenic activity of benzopyrene (*70*).

### *Other precautions*

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Flos Caryophylli should not be administered during pregnancy or lactation or to children without medical supervision.

## Adverse reactions

Allergic contact dermatitis has been reported in patients who were regularly exposed to Flos Caryophylli or who already had dermatitis of the fingertips (*71*).

## Dosage forms

Crude drug, extracts, tincture (1:5, 25% ethanol), lozenges and mouthwash. Store in a well-closed container, protected from light (*1*, *5*).

## Posology

(Unless otherwise indicated)

Daily dosage: crude drug 3–5 g as an infusion (preferably taken hot), three times daily; 25% ethanol extract (1 : 1) 3–5 ml; tincture (1 : 5, 25% ethanol) 10–25 ml (*2*).

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# Rhizoma Cimicifugae Racemosae

## Definition

Rhizoma Cimicifugae Racemosae consists of the dried rhizomes and roots of *Cimicifuga racemosa* (L.) Nutt. (Ranunculaceae) (*1*)[1].

## Synonyms

*Actaea gyrostachya* Wender, *A. orthostachya* Wender, *A. monogyna* Walt., *A. racemosa* L., *Bortrophis actaeoides* Raf., *B. serpentaria* Raf., *Christophoriana canadensis racemosa* Gouan, *Cimicifuga racemosa* (Torr) Bart., *C. serpentaria* Pursh, *Macrotis racemosa* Sweet, *M. serpentaria* Raf., *Macrotrys actaeiodes* Raf. (*4–6*).

## Selected vernacular names

Actée à grappes, black cohosh, black root, black snakeroot, bugbane, bugwort, bugwort rattleroot, cimicifuga, cohosh bugbane, Frauen Wurzel, herbe aux punaises, macrotnys, macrotys, macroty's, natsushirogiku, Qatil el baq, racine d'actée à grappes, rattle root, rattle snake root, rattle top, rattleweed, rich weed, schwarze Schlangenwurzel, squaw root, squawroot, Traubensilberkerze, Wanzenkraut, zilberkaars (*7–9*).

## Geographical distribution

Indigenous to eastern North America (*9*).

## Description

A perennial herb, up to 1–2.5 m high; subterranean part consists of a thick, knotted rhizome system. Leaves compound, pinnate, up to 7 cm long; leaflets serrate along the margin, subcordate to subcuneate at the base. Inflorescence a long, wand-like raceme of white flowers with numerous stamens (*9*, *10*).

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[1] Rhizomes and roots of *Cimicifuga heracleifolia* Kom., *C. dahurica* (Turcz.) Maxim. or *C. foetida* L. are referred to as Rhizoma Cimicifugae in the *Pharmacopoeia of the People's Republic of China* (*2*). Rhizomes and roots of *C. simplex* Warm. and related species are referred to under the same name in *The Japanese pharmacopoeia* (*3*).

## Plant material of interest: dried rhizomes and roots

### General appearance

Mixture of entire and broken dried rhizomes and roots. Rhizome dark-brown, hard, sub-cylindrical and somewhat knotted; 1–2.5 cm in diameter and 2–15 cm long, with numerous, closely-arranged, upright or curved branches, each terminating in the remains of a bud or a circular, cup-shaped scar; branches about 1 cm in diameter and up to 3 cm long, marked with distinct, encircling leaf scars; fracture horny; transverse surface showing a thin outer bark surrounding a ring of numerous pale, narrow wedges of vascular tissue alternating with dark medullary rays; a large central pith.

Roots attached to under surface of the rhizome or, more usually, broken off leaving circular scars. Roots dark brown, 1–3 mm in diameter, brittle, nearly cylindrical or obtusely quadrangular, longitudinally wrinkled; fracture short; transverse surface showing a distinct cambium line separating the wide outer bark from the central region composed of 3–6 wedges of lignified xylem tissue united at their apices and separated by broad, non-lignified medullary rays (*1*, *9*).

### Organoleptic properties

Odour: slight; taste: slightly bitter (*1*, *9*).

### Microscopic characteristics

Rhizome: yellowish-brown, suberized epidermis, several layers of starch- and resin-containing cortical parenchyma, 2 circles of open, collateral, fibrovascular bundles, the outer bundles being smaller than the inner; medullary rays separate the bundles and contain starch grains, spherical or polygonal, simple or 2–3 or even up to 6 compound; individual grains 3–15 μm in diameter with central slit-shaped hilum. Xylem contains tracheae with bordered pits and numerous strongly lignified wood fibres; and a central pith with cells resembling those of the cortex.

Root: thin epidermis, a cortex, separated into 2 zones by a distinct endodermis, and 4–6, occasionally 3, open, collateral fibrovascular bundles separated by broad, wedge-shaped medullary rays (*1*, *9*).

### Powdered plant material

Light brown, odourless with a bitter taste; abundant starch grains, often occurring in masses in numerous fragments of thin-walled parenchyma; groups of small, lignified vessels with closely arranged bordered pits or, less frequently, with reticulate thickening; lignified thin-walled fibres and xylem parenchyma; fragments of brown suberized cells with thickened walls (*1*).

## General identity tests

Macroscopic and microscopic and microchemical examinations (*1, 9*), and thin-layer chromatography for the presence of characteristic flavonoids and phenolic acids (*1, 11*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

### *Foreign organic matter*

Not more than 5% stem bases and not more than 2% other foreign matter (*1*).

### *Total ash*

Not more than 10% (*1*).

### *Acid-insoluble ash*

Not more than 4% (*1*).

### *Water-soluble extractive*

Not less than 10% (*1*).

### *Loss on drying*

Not more than 12% (*5*).

### *Pesticide residues*

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

### *Heavy metals*

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

### *Radioactive residues*

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

### *Other purity tests*

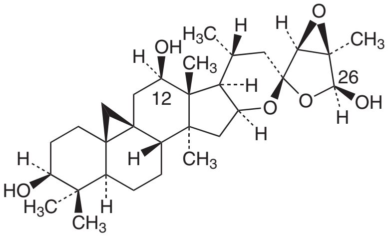
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

## Chemical assays

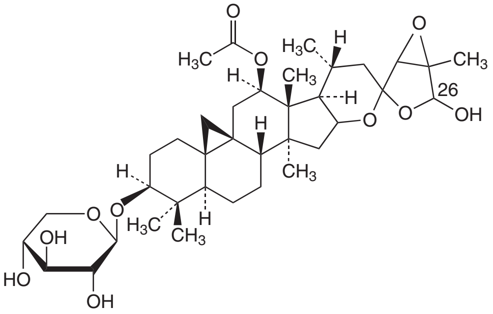
Qualitative assessments may be based on the triterpene and isoflavonoid content. Concentration ranges and quantitative methods need to be established. A high-performance liquid chromatography method is available for the quantitative analysis of flavones (*15*).

## Major chemical constituents

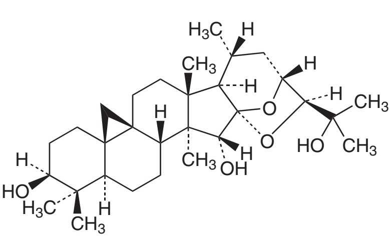
The major and characteristic constituents include the cycloartanol-based triterpenes acteol, acetylacteol, 26-deoxyacteol, cimigenol, actein, 26-deoxyactein and cimicifugoside. (*E*)-Isoferulic acid and the isoflavone formononetin are also found (*4, 15–17*). However, the latter compound could not be detected in alcohol extracts of the root (*15*). The structures of the representative constituents are presented below.



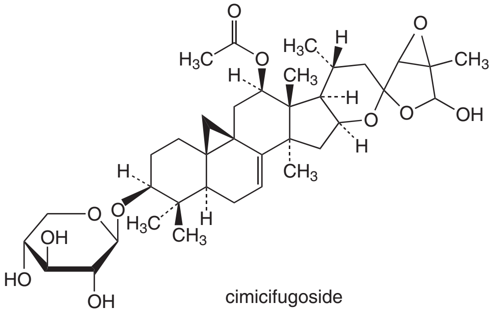
acteol



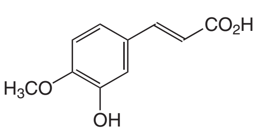
actein



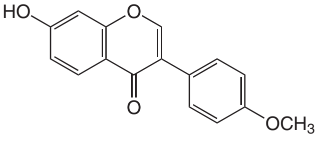
cimigenol



cimicifugoside



(*E*)-isoferulic acid



formononetin

# Medicinal uses

## Uses supported by clinical data

Treatment of climacteric symptoms such as hot flushes, profuse sweating, sleeping disorders and nervous irritability (*18–26*).

## Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of premenstrual syndrome and dysmenorrhoea (*27*, *28*).

## Uses described in folk medicine, not supported by experimental or clinical data

Treatment of coughs, dyspepsia, epilepsy, intercostal myalgia, rheumatoid arthritis, sciatica, snake bites, tinnitus and whooping cough (*1*, *8*, *9*, *28*, *29*).

# Pharmacology

## Experimental pharmacology

### Estrogenic activity

The estrogenic effects of Rhizoma Cimicifugae Racemosae are controversial, and have been assessed both in vitro and in vivo. The in vitro proliferation of human mammary carcinoma cells (cell line 435) was measured after treatment with an isopropyl alcohol extract of the rhizome. Treatment using concentrations below 2.5 μg/ml did not enhance growth of the cells. However, concentrations of 2.5 μg/ml and above significantly inhibited cell proliferation (*30*). Similar results were obtained using the estrogen receptor-positive human mammary carcinoma cell line MCF-7. When these cells were treated with a 40% isopropyl alcohol extract of the rhizome at concentrations ranging from 1 ng/ml to 100 μg/ml, the extract induced a dose-dependent inhibition of cell proliferation and also augmented the antiproliferative effects of tamoxifen (*31*). An extract of the rhizome (extract not specified) was tested in vivo for possible estrogenic effects in female rats. The extract was added to a standard liquid diet and fed to ovariectomized rats daily for 3 weeks. An increase in uterine weight was observed, along with an increase in serum ceruloplasmin levels, suggesting estrogenic activity of the extract (*32*). However, in a short-term study, intragastric or subcutaneous administration of a 50% ethanol extract of the rhizome (30, 300 or 3000 mg/kg body weight) to immature mice daily for 3 days did not have any estrogenic effects, as assessed by changes in uterine weight and vaginal cytology (*33*). Constituents of a chloroform fraction, isolated from a methanol extract of the rhizome, bound to the estrogen receptors of isolated rat uteri in vitro. Formononetin, a minor constituent of the extract, showed a low binding affinity to the estrogen receptor (11.5 mmol/l) (*34*). The effects of formononetin and a dichloromethane extract of the rhizome on luteinizing hormone secretion were tested in vivo (*35*). Ovariectomized rats received nine intraperitoneal injections over 5 days (equivalent to a total

dose of 10 mg formononetin or 108 mg extract). The extract, but not formononetin, reduced the serum concentration of luteinizing hormone (*34, 35*). Intraperitoneal (but not intragastric) administration of a chloroform (140 mg), 60% ethanol (0.3 ml) or dichloromethane (27 mg) extract of the rhizome reduced the serum concentration of luteinizing hormone in ovariectomized rats after 3–3.5 days of treatment (*34, 36, 37*). Serum follicle-stimulating hormone and prolactin levels, however, were not affected (*34*). Intragastric administration of a 95% ethanol extract of the rhizome (0.05 ml/animal daily) had no effect on genital functions in female mice (*38*).

The effects of estradiol on estrogen-dependent brain and uterine functions were compared with those of a dichloromethane fraction of a hydroalcoholic rhizome extract. Daily injection of the extract (60 mg/rat) or estradiol for 3 weeks reduced serum luteinizing hormone levels, but only estradiol increased uterine weight. Up-regulation of estrogen receptor-α gene expression was observed in MCF-7 mammary carcinoma cells treated with either the extract (35 μg/ml) or estradiol. The results suggest that the dichloromethane fraction of the extract may act as a selective modulator of the estrogen receptor (*39*).

### Anti-inflammatory activity

Subcutaneous injection of an ethanol extract of the crude drug (100 mg/kg body weight) reduced carrageenan-induced footpad oedema in rats by 32% (*40*).

## *Clinical pharmacology*

### Climacteric symptoms

The following studies were all performed using oral administration of either a 40% isopropyl alcohol or 60% ethanol extract of Rhizoma Cimicifugae Racemosae.

In a placebo-controlled clinical trial, 110 women with climacteric symptoms were treated with the ethanol extract (8 mg daily) for 2 months. Although a significant reduction in serum luteinizing hormone levels was observed in the treated group ($P < 0.01$), there was no effect on follicle-stimulating hormone levels (*37*).

A 12-week double-blind, placebo-controlled study of 80 women (aged 45–58 years) compared the efficacy of the rhizome extract (8 mg daily) with either conjugated estrogens (0.625 mg daily) or placebo for the treatment of climacteric symptoms and vaginal atrophy. The group treated with the extract showed a greater reduction in climacteric symptoms than groups treated with either conjugated estrogens or placebo, as demonstrated by a significant reduction in both the Kupperman Index and Hamilton Rating Scale for Anxiety (Hamilton Anxiety Rating Scale), and by the proliferative status of the vaginal epithelium ($P < 0.001$) (*23*).

The efficacy of the isopropyl alcohol extract for the treatment of climacteric symptoms induced by hysterectomy was assessed in a randomized comparison trial without controls. Sixty women under the age of 40, who had

undergone a hysterectomy, but retained one ovary, were treated daily with either the extract (8 mg), estriol (1 mg), conjugated estrogens (1.25 mg) or an estrogen–progesterone combination. After 4, 8, 12 and 24 weeks of treatment, a significant decrease in climacteric symptoms was reported by the patients in all treatment groups ($P < 0.01$). This was verified by a reduction in a modified Kupperman index. Conjugated estrogens or the estrogen–progesterone combination appeared to be slightly more effective than the extract; however, no significant difference between the three treatments was observed. Serum levels of luteinizing hormone and follicle-stimulating hormone did not change significantly in any of the groups ($P > 0.05$) (*20*).

In a study without controls of 50 women with climacteric complaints, after administration of the ethanol extract (40 drops twice daily for 12 weeks), patients with moderate symptoms required no further treatment (*25*).

A randomized controlled trial involving 60 women aged 45–60 years compared the efficacy of the ethanol extract with hormone replacement therapy (0.6 mg conjugated estrogens) or 2 mg diazepam for the treatment of climacteric symptoms. Clinical assessment of the patients was based on three indicators: the menopause index (for hot flushes, nocturnal sweating, nervousness, headache and palpitations), and the Hamilton Anxiety Rating Scale and self-assessment depression scale (for psychological symptoms). Patients were treated with either the extract (40 drops twice daily), conjugated estrogens (0.625 mg daily) or diazepam (2 mg daily) for 12 weeks. All three forms of therapy reduced all three indicators. The extract and conjugated estrogens also reduced atrophic changes in the vaginal mucosa (*26*).

In a study without controls, 36 women with climacteric symptoms were treated with the ethanol extract (40 drops) twice daily for 12 weeks. A significant decrease in the average values of the Kupperman index was reported ($P < 0.001$), and an increase in the values of the Clinical Global Impression scale was observed (*18*).

A placebo-controlled clinical trial assessed the efficacy of a rhizome extract for the treatment of 82 women with climacteric symptoms. In the group treated with the extract, 31 women reported a considerable decrease in symptoms, while 10 women with severe climacteric symptoms did not show improvement. In the placebo group, a reduction of symptoms was seen in four women; symptoms were unchanged in 37 women (*19*).

In a study without controls, 50 women with climacteric symptoms, who had received at least one or two intramuscular injections of estradiol valerate (4 mg) and prasterone enantate (200 mg) during 1–2 months prior to the trial, were treated with the isopropyl alcohol extract (2 tablets twice daily) for 6 months. The therapeutic results were rated as good to very good in 41 of the patients: during the treatment period 28 required no further injections, 21 patients required one injection and one patient required two injections. The Kupperman index decreased significantly ($P < 0.001$), indicating successful treatment of symptoms (*22*).

A multicentre, drug-monitoring study without controls of 629 women with climacteric symptoms assessed the efficacy of the ethanol extract (40 drops

twice daily) for 8 weeks. Symptoms improved in over 80% of all patients after 6–8 weeks of treatment (*24*).

A 6-month randomized, double-blind clinical trial compared two different doses of the isopropyl alcohol extract (40 and 127 mg daily) in 152 women with climacteric symptoms. A decrease in the Kupperman index was observed after 2 weeks in both treatment groups. Both dosages showed similar levels of efficacy and safety. After 6 months, approximately 90% of patients had responded to the treatment. No effects on vaginal cytology or the levels of luteinizing hormone, follicle-stimulating hormone, sex hormone binding-globulin, prolactin and estradiol were observed (*21*, *41*, *42*).

A review of eight clinical trials assessed the efficacy of extracts of the crude drug for the alleviation of climacteric symptoms in women. It concluded that preparations of the rhizome may be a safe and effective alternative to estrogen replacement therapy for patients for whom the replacement therapy is contraindicated or refused (*43*).

### General gynaecological disorders

Five case studies have described the successful use of a 40% isopropyl alcohol or 60% ethanol extract of the rhizome in the treatment of a total of 833 women with gynaecological disorders (e.g. climacteric symptoms) and menstrual disorders (e.g. primary or secondary amenorrhoea, and premenstrual disorders) (*44–48*).

## Contraindications

Owing to its potential estrogenic effects (*39*) and the lack of data on its safety, Rhizoma Cimicifugae Racemosae should not be used during pregnancy or lactation, or in children under the age of 12 years.

## Warnings

No information available.

## Precautions

### *Carcinogenesis, mutagenesis, impairment of fertility*

A 40% isopropyl alcohol extract of the crude drug was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 or TA100 (*16*).

### *Pregnancy: teratogenic effects*

Intragastric administration of up to 2 g/kg body weight of the crude drug, as a component of two traditional Chinese medicines, to pregnant rats daily on days 7–17 of gestation was not teratogenic (*49*, *50*). (See also Contraindications.)

### *Pregnancy: non-teratogenic effects*

See Contraindications.

### *Nursing mothers*

See Contraindications.

### *Paediatric use*

See Contraindications.

### *Other precautions*

No information available on general precautions or precautions concerning drug interactions or drug and laboratory test interactions.

## Adverse reactions

Minor gastrointestinal upset and headache (*19*, *23–25*).

## Dosage forms

Crude drug, and isopropyl alcohol or ethanol extracts (*16*). Store in a well-closed container, protected from light and moisture.

## Posology

(Unless otherwise indicated)
Daily dosage: 40–60% isopropyl alcohol or ethanol extracts of the crude drug (*18–20*, *22–26*, *37*, *42*), corresponding to 40 mg drug (*27*).

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# Folium cum Flore Crataegi

## Definition

Folium cum Flore Crataegi consists of the dried flower-bearing branches of *Crataegus monogyna* Jacq. (Lindm), *C. laevigata* (Poir.) DC, their hybrids or, more rarely, other *Crataegus* species (Rosaceae).[1]

## Synonyms

*Crataegus monogyna* Jacq. (Lindm): *C. apiifolia* Medik. non Michx., *C. oxyacantha* L. ssp. *monogyna* Lev., *Mespilus elegans* Poir., *M. monogyna* All., *M. monogyna* Ehrh. (*3*).

*Crataegus laevigata* (Poir.) DC: *C. oxyacantha* L., *C. oxyacantha* L. ssp. *polygala* Lev., *C. oxyacanthoides* Thuill, *Mespilus oxyacantha* (Gartn.) Crantz. (*1, 3, 4*).

## Selected vernacular names

Aubeline, aubepine, biancospino, calabrice, calavrice, eenarijlige meidorn, eenstijlige meidorn, eingriffeliger Weissdorn, Einkern-Weissdorn, épine blanche, espinero, espino blanco, espino majuelo, galagonya virágzó ágvég, hagdorn, hagedorn, harthorne, haw, hawthorn, hedge thorn, majuelo, may, May thorn, Mehlbeerbaum, Mehldorn, seiyosanzashi, shanzha, sorkh valik, spina, Stumpf gelappter Weissdorn, Weissdorn, whitethorn, za bur, zu'rurr el awdiyah, zweigriffeliger Weissdorn, Zweikern-Weissdorn (*1, 3, 5–8*).

## Geographical distribution

Common to the temperate areas of the northern hemisphere, including eastern areas of North America, parts of South America, east Asia and Europe (*9, 10*).

## Description

*Crataegus monogyna*: a thorny shrub; leaves bright green with 3 or 5 acute lobes, deeper and further apart than those of *C. laevigata*. Flowers, grouped into

[1] Fructus Crataegi is included in the *European pharmacopoeia* (*1*) and in the pharmacopoeia of the People's Republic of China (*2*). However, clinical and pharmacological data for this plant part are insufficient to justify monographing at this time.

branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a monocarpellate, brownish-green receptacle; floral peduncles and sepals pubescent, stamen with black anthers and 1 style (*1, 9*).

*Crataegus laevigata*: a thorny shrub; twigs glabrescent, brown; leaves bright green, obovate, with 3, 5 or 7 shallow, obtuse lobes. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a bi- or tricarpellate receptacle; floral peduncles and sepals glabrous, stamens with red anthers and 2–3 styles; fruits deep red, globose or ellipsoid (*9, 11*).

## Plant material of interest: dried leaf with flower

### *General appearance*

*Crataegus monogyna*: leaves bright green with 3 or 5 acute lobes, deeper and further apart than those of *C. laevigata*, with secondary venation curved outwards. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a monocarpellate, brownish-green receptacle; floral peduncles and sepals pubescent, anthers black with 1 style; sepals lanceolate, acuminate, falling over the ovary after flowering (*1, 9*).

*Crataegus laevigata*: leaves bright green with 3, 5 or 7 shallow, obtuse, converging lobes, with secondary venation curved inward. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a bi- or tricarpellate receptacle; floral peduncles and sepals glabrous, stamens with red anthers and 2–3 styles.

### *Organoleptic properties*

Odour: characteristic, faint; taste: slightly bitter-sweet, astringent (*12–15*).

### *Microscopic characteristics*

Leaf dorsoventral; cells of upper epidermis polygonal, straight-walled with striated cuticle, those of lower epidermis more sinuous; anomocytic stomata on lower epidermis only; covering trichomes on both epidermises but more numerous on the lower, which are long, tapering, unicellular or very occasionally uniseriate with 2 cells, walls moderately thickened; cluster crystals or groups of small prismatic crystals of calcium oxalate in the cells along the veins. Epidermis of floral pedicel and receptacle contain abundant covering trichomes similar to those on the leaf, but longer and more undulating; calyx with numerous anomocytic stomata on the outer epidermis, inner epidermis with a striated cuticle; epidermal cells of corolla distinctly papillose; fibrous layer of anther with characteristic thickenings; pollen grains spherical to elliptical, up to 45 µm in diameter, with 3 germinal pores and faintly granular exine. Epidermal cells

of stem have thickened anticlinal outer walls; cortex parenchymatous with prismatic and cluster crystals of calcium oxalate; dense groups of small, tightly packed pericyclic fibres with much thickened and lignified walls; xylem completely lignified, composed of scattered vessels, thick-walled fibres and parenchyma separated by distinct medullary rays containing brown-coloured matter; larger vessels with bordered pits, smaller elements with annular or spiral thickening; central pith parenchymatous and lignified, cells with moderately thickened walls and numerous pits (*12*, *15*).

### *Powdered plant material*

Yellowish-green. Unicellular covering trichomes, usually with a thick wall and wide lumen, almost straight or slightly curved, pitted at the base; fragments of leaf epidermis with cells which have sinuous to polygonal anticlinal walls and large anomocytic stomata surrounded by 4–7 subsidiary cells; parenchymatous cells of mesophyll containing cluster crystals of calcium oxalate, usually 10–20 μm in diameter; cells associated with veins contain groups of small prismatic crystals. Petal fragments showing rounded polygonal epidermal cells, strongly papillose, thick walls with clearly visible wavy striations in the cuticle; anther fragments showing endothecium with an arched and regularly thickened margin. Stem fragments containing collenchymatous cells, bordered, pitted vessels and groups of lignified sclerenchymatous fibres with narrow lumina. Numerous spherical to elliptical or triangular pollen grains up to 45 μm in diameter, with 3 germinal pores and a faintly granular exine (*1*).

## General identity tests

Macroscopic and microscopic examinations, thin-layer chromatography (*1*, *7*), and microchemical test for the presence of procyanidins (*7*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*16*).

### *Foreign organic matter*

Not more than 8% lignified branches with a diameter greater than 2.5 mm (*1*) and not more than 2% other foreign matter (*1*, *15*).

### *Total ash*

Not more than 10% (*1*).

### *Loss on drying*

Not more than 10% (*1*).

### *Pesticide residues*

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*17*). For other pesticides, see the *European pharmacopoeia* (*17*), and the WHO guidelines on quality control methods for medicinal plants (*16*) and pesticide residues (*18*).

### *Other purity tests*

Chemical, acid-insoluble ash, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

### *Heavy metals*

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*16*).

### *Radioactive residues*

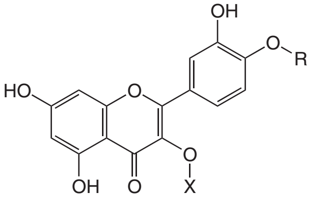
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*16*) for the analysis of radioactive isotopes.

## Chemical assays

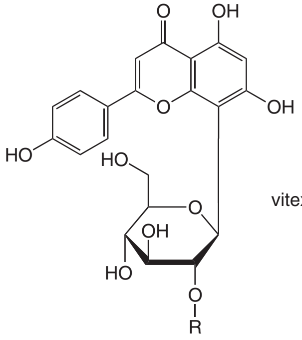
Contains not less than 1.5% of flavonoids, calculated as hyperoside (*1*), and not less than 0.6% of flavone C-glycosides, calculated as vitexin (*14*), determined by spectrophotometry at 410 and 336 nm, respectively (*1*). A high-performance liquid chromatography method is also available (*19*).

## Major chemical constituents

The major constituents are flavonoids (rutin, hyperoside, vitexin, vitexin-2″ rhamnoside, acetylvitexin-2″ rhamnoside) and related proanthocyanidins (*19, 20*). In the inflorescence, flavonol glycosides, mainly in the form of hyperoside, spiraeoside and rutin, are present. The primary flavonoid derivatives in the leaves are *epi*-catechin (*epi*-catechol) and/or catechin (catechol), and the related procyanidins formed during condensation of 2–8 monomeric units of the above catechins (*19–22*), together with oligomeric procyanidins (*23*). The presence of simple phenolic acids (e.g. chlorogenic and caffeic acids) has also been reported. Of the non-phenolic constituents, pentacyclic triterpenes (e.g. ursolic and oleanolic acids) and the 2-α-hydroxy derivative of oleanolic acid, known as crataegolic acid, are among the characteristic components (*4*). The structures of the characteristic constituents are presented below.

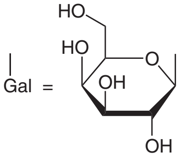


| | R | X |
|---|---|---|
| hyperoside | H | Gal |
| spiraeoside | Glc | H |
| rutin | H | Rha-Glc |

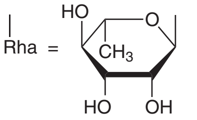


vitexin
R = H

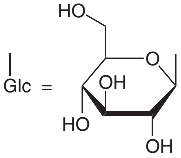
vitexin 2″-rhamnoside
R = Rha



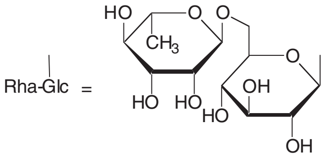
β-D-galactopyranosyl



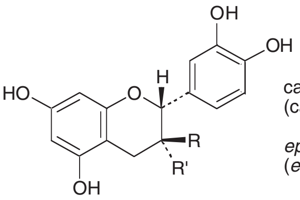
α-L-rhamnopyranosyl =
6-deoxy-α-L-mannopyranosyl



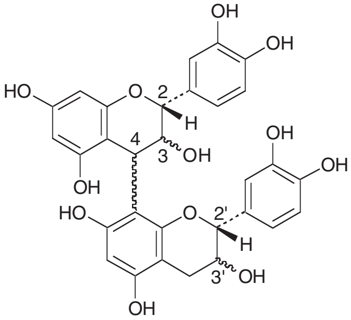
β-D-glucopyranosyl



6-deoxy-α-L-mannopyranosyl-(1→6)-
β-D-glucopyranosyl



| | R | R′ |
|---|---|---|
| catechin (catechol) | OH | H |
| *epi*-catechin (*epi*-catechol) | H | OH |



| procyanidin | 2 | 2′ | 3 | 3′ | 4 |
|---|---|---|---|---|---|
| $B_1$ | α-(*R*) | α-(*R*) | α-(*R*) | β-(*S*) | β-(*R*) |
| $B_2$ | α-(*R*) | α-(*R*) | α-(*R*) | α-(*R*) | β-(*R*) |
| $B_3$ | α-(*R*) | α-(*R*) | β-(*S*) | β-(*S*) | α-(*S*) |
| $B_4$ | α-(*R*) | α-(*R*) | β-(*S*) | α-(*R*) | α-(*S*) |

## Medicinal uses

### *Uses supported by clinical data*

Treatment of chronic congestive heart failure stage II, as defined by the New York Heart Association (*24–34*).

### *Uses described in pharmacopoeias and in traditional systems of medicine*

Support of cardiac and circulatory functions (*35*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

As an antispasmodic agent in the treatment of asthma, diarrhoea, gall bladder disease and uterine contractions, and as a sedative for the treatment of insomnia (*5*).

## Pharmacology

### *Experimental pharmacology*

#### Inotropic effects

Positive inotropic effects of Folium cum Flore Crataegi and its constituents have been demonstrated both in vitro and in vivo. These effects are generally attributed to the flavonoid and procyanidin constituents of the leaves with flowers (*3, 36–38*). A hydroalcoholic extract of the flowers with leaves, flavonoid and procyanidin fractions of the extract, and isolated constituents (e.g. biogenic amines, crataegolic acid, *epi*-catechin, hyperoside, luteolin 7-glucoside, rutin and vitexin) all have positive inotropic effects, and prolong the refractory period in cardiac myocytes, isolated papillary muscles and isolated guinea-pig hearts (*36–48*). In isolated guinea-pig hearts perfused at constant pressure, 3 µg/ml of a standardized extract increased the contractility of the heart by 9.5% (*40*). In isolated, electrically stimulated strips of failing human left ventricular myocardium, a standardized extract (18.75% oligomeric procyanidins) increased the force of contraction at concentrations higher than 10 µg/ml; a 100 µg/ml extract improved the force–frequency relationship (*39*). A standardized extract of the leaves and flowers increased the contractility of myocardial cells by 153%, at a concentration of 120 µg/ml (*44*). An aqueous extract of the leaves with flowers, two proanthocyanidin fractions and two flavonoid fractions of the extract dilated coronary blood vessels, and had positive inotropic effects on isolated guinea-pig hearts (extract or fraction: 0.05 mg/ml) (*41*).

#### Chronotropic effects

Intragastric administration of a macerate or fluidextract of the shoots, flowers or leaves to rats (12.5–25.0 mg/kg body weight) significantly inhibited arrhythmias induced by aconitine, calcium chloride or chloroform/epinephrine

($P < 0.05$) (*49, 50*). The extracts also reduced blood pressure in rats at the same dosage (*49, 50*). Aconitine-induced arrythmias were also inhibited after intravenous administration of a 95% ethanol extract of the bark and leaves (50 mg/kg body weight) to rabbits (*51*). Intravenous administration of a flavonoid-enriched extract of the leaves and flowers to rabbits (20 mg/kg body weight) or rats (2 mg/kg body weight) inhibited barium chloride-induced arrhythmias (*52, 53*). Intravenous administration of a standardized extract (containing 18.75% oligomeric procyanidins) to anaesthetized dogs (7.5–30.0 mg/kg body weight) increased maximum left ventricular contraction velocity by 16.8–31.1% (*54*).

An aqueous extract improved cardiac performance during reperfusion, reduced lactate levels and accelerated energy metabolism in reperfused ischaemic rat heart. No increase in coronary blood flow was observed (*55*). Intragastric administration of single doses of a standardized extract (containing 18.75% oligomeric procyanidins) of the leaves with flowers (100 mg/kg body weight) or an oligomeric procyanidin-enriched fraction (20 mg/kg body weight) daily to rats protected against perfusion-induced arrhythmias, hypotensive crisis and mortality (*56, 57*). The oligomeric procyanidin-enriched fraction did not decrease the reperfusion-induced elevation of creatine kinase plasma levels (*57*). Administration of powdered leaves and flowers to rats (2% of diet) reduced the release of lactate dehydrogenase after perfusion-induced heart ischemia (*58*).

### Effect on coronary blood flow

Intragastric administration of an oligomeric procyanidin fraction of a standardized leaf and flower extract to dogs at a dose of 12–70 mg/kg body weight, three times daily for 60 days, increased myocardial blood flow (*59, 60*). Intravenous injection of an aqueous or 95% ethanol extract of the flowers increased coronary blood flow and cardiac output, and decreased peripheral resistance in both dogs and guinea-pigs (*61–63*). Administration of a flavonoid-enriched extract to cats and rabbits increased coronary blood flow by 48% and 163%, respectively, and reduced pituitrin-induced coronary insufficiency in rabbits (*52*). Intravenous administration of a leaf with flower extract to cats (10 mg/kg body weight) or rabbits (20 mg/kg body weight) dilated coronary blood vessels, and improved coronary blood flow (*53*).

### Effect on action potential

A leaf preparation (10 mg/l) prolonged the duration of the action potential and delayed the recovery of $V_{max}$ in isolated guinea-pig papillary muscle (*42*). The electrophysiological correlation between the increase in the contraction amplitude of isolated canine papillary muscles, and vasodilation in isolated human coronary arteries, was measured after application of an extract of the leaves with flowers. The cardiac action potential significantly increased in duration and overshoot, and maximal depolarization ($P < 0.001$). Hyperpolarization of

the resting membrane of normal and arteriosclerotic vascular smooth muscle cells of the human coronary artery was observed after treatment with flavonoids isolated from the extract (0.1 and 100 µmol/l). The isometric wall tension decreased in both normal and arteriosclerotic vessels. The increase of peak-to-plateau repolarization in cardiac action potential and hyperpolarization of vascular smooth muscle suggest that the extract acts as a potassium channel agonist (*64, 65*).

### Antihypertensive effects

In various animal models, a decrease in peripheral vascular resistance and hypertension occurred after treatment with leaf and/or flower extracts (*50, 54, 66–69*). Intravenous administration of a standardized fluidextract of the leaves with flowers (equivalent to 6 mg of procyanidins/kg body weight) to anaesthetized normotensive dogs decreased norepinephrine-induced elevation of blood pressure. The extract (equivalent to 0.03 mg procyanidins/ml) also had β-blocking activity and inhibited epinephrine-induced tachycardia in isolated frog hearts (*69*). Hyperoside, isolated from an extract of the leaves and flowers, administered either intravenously at a dose of 1 mg/kg body weight or by infusion at 0.1 mg/kg body weight/min for 30 min, decreased blood pressure in anaesthetized dogs (*68*). Intravenous administration of an aqueous extract of the leaves (average dose 31 mg/kg body weight) decreased the systolic, diastolic and mean blood pressure in normotensive anaesthetized rats (*66*). Acute or chronic intragastric administration of a fluidextract or a glycerol/ethanol extract reduced arterial blood pressure in normotensive rats and in rats with desoxycorticosterone acetate-induced hypertension (*50*). Intragastric administration of a standardized extract (300 mg/kg body weight daily) decreased blood pressure by 9 mm Hg (1.20 kPa) (*67*). Intravenous administration of a standardized extract (containing 18.75% oligomeric procyanidins) to anaesthetized rats (30 mg/kg body weight) or dogs (15 mg/kg body weight) decreased total peripheral resistance and arterial blood pressure (*54*).

### Anti-inflammatory effects

Both free radical production and lipid peroxidation are involved in various pathological processes, including cardiac ischaemia. As determined by in vitro studies, Folium cum Flore Crataegi has free radical scavenging and antioxidant activities. A standardized extract (containing 18.75% oligomeric procyanidins) and an oligomeric procyanidin-fraction of the extract inhibited lipid peroxidation ($IC_{50}$ 0.48 µg/ml (extract), 0.3 µg/ml (fraction)), and the activity of human neutrophil elastase ($IC_{50}$ 4.75 µg/ml (extract), 0.84 µg/ml (fraction)) (*56*). A 70% methanol extract of the flower buds inhibited lipid peroxidation in rat liver microsomes ($IC_{50}$ 23 mg/l) (*70, 71*). Both phenolic and flavonoid-enriched fractions of extracts of the leaves and flowers had antioxidant activity in vitro (*70–72*).

### Effect on signal transduction

An aqueous or methanol extract of the leaves with flowers, as well as hyperoside, vitexin and vitexin rhamnoside, inhibited the activity of cyclic AMP-dependent phosphodiesterase isolated from guinea-pig or rat heart (*73, 74*). Both luteolin 7-glucoside and rutin were also active (*75*). Hydroalcoholic extracts of the flowers and flower heads inhibited the formation of thromboxane $A_2$ and prostaglandin $I_2$ in rabbit cardiac tissues in vitro, thus indicating an anti-inflammatory effect of the extracts (*76, 77*). A standardized extract (containing 18.75% oligomeric procyanidins) displaced $^3$H-ouabain bound to sodium- and potassium-activated adenosine triphosphatase (*39*).

### Anticontractile effects

An aqueous extract of the flowers inhibited barium chloride-induced contractions in rabbit intestine in vitro (*78*). A flavonoid-enriched extract of the leaves with flowers inhibited both histamine- and nicotine-induced contractions in rabbit intestine in vitro and partially inhibited contractions induced by barium chloride, acetylcholine or serotonin ($ED_{50}$ 0.02 mg/ml) (*52*). Intravenous administration of a flavonoid-enriched extract of the leaves with flowers to cats (20 mg/kg body weight) inhibited contractions in intestinal smooth muscle, and intraperitoneal injection (400 mg/kg body weight) inhibited acetic acid-induced writhing in mice (*52*).

### Sedative effects

Sedative effects have been observed in various animal models after intragastric administration of leaf with flower extracts (*79, 80*). A 60% ethanol extract of the flowers increased hexobarbital-induced sleeping times, and decreased spontaneous motility and exploratory behaviour in female mice (800 mg/kg body weight) (*80*).

### Diuretic effects

A flavonoid-enriched fraction of a flower extract had diuretic activity in dogs (50 mg/kg body weight) (*81*).

## Toxicology

Single-dose toxicity studies have demonstrated that rats and mice tolerate 3 g/kg body weight, by gastric lavage, of a standardized hydroalcoholic extract of the leaves with flowers (containing 18.75% oligomeric procyanidins) without any clinical symptoms of toxicity. The intraperitoneal median lethal dose ($LD_{50}$) was 1.17 g/kg body weight in rats and 750 mg/kg body weight in mice. No toxic effects were observed in a repeat-dose toxicity study in which rats and dogs were given a standardized extract (containing 18.75% oligomeric procyanidins) at doses of 30, 90 and 300 mg/kg body weight daily by the intragastric route for 26 weeks (*82*).

## *Clinical pharmacology*

### Cardiac insufficiency

Review of the pharmacological and clinical data indicates that standardized extracts of Folium cum Flore Crataegi increase myocardial performance, improve myocardial circulatory perfusion and tolerance in cases of oxygen deficiency, have antiarrhythmic effects and reduce afterload (*29*). Positive therapeutic effects of Folium cum Flore Crataegi in patients with characteristic symptoms of an activated sympathoadrenergic system, such as hypertension, tachycardia and arrhythmia (also characteristic of cardiac insufficiency stage II, as defined by the New York Heart Association (*25–34*)), have also been demonstrated (*30*). Furthermore, numerous clinical trials with and without controls have assessed the therapeutic efficacy of Folium cum Flore Crataegi extracts for the treatment of cardiac insufficiency stage II (*25–34*). The investigations were performed with a dried 70% methanol or 45% ethanol standardized extract (containing 2.2% flavonoids or 18.75% oligomeric procyanidins, respectively) of the leaves with flowers (*30*). The dosage ranged from 160 to 900 mg extract daily for 4–8 weeks. Evaluation of efficacy of the extracts was based on the following criteria: anaerobic threshold (*27*); Clinical Global Impression Scale (*31*, *32*); exercise tolerance (*25*, *26*, *28*, *31*, *32*, *34*); ventricular ejection fraction (*26*, *33*); quality of life and improvement of subjective symptoms (defined by the New York Heart Association) (*26–28*, *31–34*) and pressure/rate product (*26*, *28*, *31*, *32*, *34*). Although improvements were seen, no long-term trials have assessed the effects of Folium Cum Flore Crataegi on mortality rates in patients with chronic congestive heart failure.

### Exercise tolerance

A randomized, double-blind, placebo-controlled trial assessed the efficacy of the extract containing 2.2% flavonoids on exercise-induced anaerobic threshold, as measured by spiroergometry, in 72 patients. Patients were administered an oral dose of 900 mg extract or placebo daily for 8 weeks. After treatment, oxygen uptake increased significantly in the treated group ($P < 0.05$), and exercise time to anaerobic threshold increased by 30 seconds in the treated group, but by only 2 seconds in the placebo group. Significant improvements in subjective symptoms were also noted in the treated group, as compared with the placebo group ($P < 0.01$) (*27*).

The efficacy of the extract containing 2.2% flavonoids on the improvement of exercise tolerance was assessed by bicycle ergometry in patients with cardiac insufficiency stage II, in three clinical trials. In a double-blind, placebo-controlled trial of 85 patients, oral administration of 300 mg extract daily for 4–8 weeks improved working capacity; however, the difference was not significant when compared with the placebo (*25*). A double-blind, placebo-controlled trial assessed the efficacy of oral administration of 600 mg extract daily for 8 weeks in 78 patients. Patients in the treatment group had a significant improvement in exercise tolerance as compared with the placebo group

($P < 0.001$). Patients who received the extract also had lower blood pressure and heart rate during exercise, and had fewer overall symptoms, such as dyspnoea and fatigue (*31*). In the third trial, 132 patients were treated orally with 900 mg extract or 37.5 mg captopril daily for 8 weeks in a double-blind comparative study. Exercise tolerance, measured after 56 days of treatment, improved significantly in both groups ($P < 0.001$). In addition, the pressure/rate product was reduced, and the incidence and severity of symptoms such as dyspnoea and fatigue decreased by approximately 50% (*32*).

### *Pressure/rate product*

Two double-blind, placebo-controlled trials assessed the efficacy of the extract containing 18.75% oligomeric procyanidins in a total of 156 patients with stage II cardiac insufficiency. Patients were treated orally with 160 mg extract or placebo daily for 8 weeks. The main parameters measured were the pressure/rate product using a bicycle ergometer, and the score of subjective symptom status. Patients treated with the extract exhibited a significant improvement in exercise tolerance, as compared with the placebo group ($P < 0.05$), and also a decrease in subjective complaints (*28, 34*). In addition, a slight reduction in the systolic and diastolic blood pressure was noted in both groups (*28*).

### Ventricular ejection fraction

In a trial without controls involving seven patients with stages II and III cardiac insufficiency, with an angiographically determined left ventricular ejection fraction of less than 55% over a period of 4 weeks, oral administration of 240 mg extract containing 18.75% oligomeric procyanidins daily for 4 weeks increased the ventricular ejection fraction from 29.80 to 40.45%, as measured by angiography. Symptomatic complaints (Complaint List as defined by von Zerssen) also showed improvements (*33*). The effects of the extract containing 18.75% oligomeric procyanidins on haemodynamics were also investigated by radionuclide angiocardiography in a study without controls. Twenty patients with stage II cardiac insufficiency, with an angiographically determined left ventricular ejection fraction of less than 55% over a period of 4 weeks, were treated with 480 mg extract. After treatment, the ejection fraction increased from 40.18 to 43.50% at rest, and from 41.51 to 46.56% under exercise conditions. Ergometric tolerance to exercise improved, blood pressure decreased and subjective complaints were reduced (*26*).

## *Pharmacokinetics*

Absorption of a $^{14}C$-labelled oligomeric procyanidin fraction of standardized extracts of leaves with flowers was measured in mice after intragastric administration (0.6 mg). The results demonstrated that 20–30% of the total fraction, 40–81% of the trimeric procyanidins and 16–42% of the oligomeric procyani-

dins were absorbed within 1–7 hours after administration. After 7 hours, 0.6% of the radioactivity of the total fraction was eliminated by expiration and 6.4% was eliminated in the urine. Daily intragastric administration of 0.6 mg of a radiolabelled oligomeric procyanidin fraction to mice for 7 days led to an accumulation of radioactivity that was 2–3 times that in mice given a single dose (*83*).

## Contraindications

None (*84*).

## Warnings

Accurate diagnosis of stage II congestive heart failure should be obtained prior to use of Folium cum Flore Crataegi. Consult a physician if symptoms worsen, remain unchanged for longer than 6 weeks, or if water accumulates in the legs. Medical attention is absolutely necessary if pain occurs in the region of the heart, spreading out to the arms, upper abdomen or neck area, or in cases of respiratory distress (e.g. dyspnoea) (*84*).

## Precautions

### *Drug interactions*

None (*84*).

### *Drug and laboratory test interactions*

No effects in laboratory tests (i.e. serum levels of sodium chloride, potassium chloride, calcium chloride, serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, γ-glutamyl transpeptidase, total bilirubin, cholesterol and creatinin, and blood glucose levels) were observed (*34*).

### *Carcinogenesis, mutagenesis, impairment of fertility*

A standardized extract of Folium cum Flore Crataegi (containing 18.75% oligomeric procyanidins) was not mutagenic or clastogenic in the *Salmonella*/microsome assay, mouse lymphoma test, cytogenetic analysis in cultured human lymphocytes or in the mouse bone marrow micronucleus test (*82*). A fluidextract was moderately active in the *Salmonella*/microsome assay in *S. typhimurium* strain TA98 only after metabolic activation. The mutagenic activity appeared to be due to the quercetin content of the extract; however, the amount of quercetin ingested in a normal daily diet is higher than would be obtained from the extract (*85*). Intragastric administration of up to 1.6 g/kg body weight had no effect on the fertility of female and male rats or the $F_1$ generation (*86*).

### *Pregnancy: teratogenic effects*

Intragastric administration of up to 1.6 g/kg body weight of a standardized extract of Folium cum Flore Crataegi to rats and rabbits was not teratogenic (*86*).

### *Pregnancy: non-teratogenic effects*

No peri- or postnatal toxicity was observed in rats treated intragastrically with a standardized extract of Folium cum Flore Crataegi (1.6 g/kg body weight) (*86*).

### *Other precautions*

No information available on general precautions or precautions concerning nursing mothers or paediatric use. Therefore, Folium cum Flore Crataegi should not be administered during lactation or to children without medical supervision.

## Adverse reactions

None (*84*).

## Dosage forms

Crude drug for infusion and hydroalcoholic extracts (*35*). Store in a well-closed container, protected from light and moisture (*1*).

## Posology

(Unless otherwise indicated)
Daily dosage: 160–900 mg dried 45% ethanol or 70% methanol extract (drug: extract ratio 4–7 : 1) standardized to contain 18.75% oligomeric procyanidins (calculated as *epi*-catechin) or 2.2% flavonoids (calculated as hyperoside), respectively (*26–29, 31–34, 84*); 1.0–1.5 g comminuted crude drug as an infusion 3–4 times daily (*35*). Therapeutic effects may require 4–6 weeks of continuous therapy (*84*).

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# Radix Eleutherococci

## Definition

Radix Eleutherococci consists of the dried roots and rhizomes of *Eleutherococcus senticosus* (Rupr. and Maxim.) Maxim. (Araliaceae) (*1–3*).[1]

## Synonyms

*Acanthopanax senticosus* (Rupr. et Maxim.) Harms., *Hedera senticosa* (*1*, *4*, *6*).

## Selected vernacular names

Buisson du diable, chi wu cha, ciwujia, devil's bush, devil's shrub, eleuthero, eleutherococc, eleutherococoque, eleutherokokk koljucij, ezoukogi, gashi ohgap, hongmao-wujiapi, many prickle acanthopanax, pai wu cha pi, prickly eleutherococc, prickly eleutherococcus, shigoka, Siberian ginseng, Stachelkraftwurz, Stachelpanax, taiga root, Taigawurzel, thorny ginseng, thorny Russian pepperbush, touch-me-not, tsu wu cha, wild pepper, wu cha sang, wu cha seng, wu jia pi (*2*, *7*).

## Geographical distribution

Indigenous to south-east Asia, northern China, the Democratic People's Republic of Korea, Japan and the south-eastern part of the Russian Federation (*4*, *5*).

## Description

A prickly shrub, up to 4–6 m high, usually with several mostly unbranched stems; oldest stems may be unarmed, while the youngest are densely covered with flexible prickles. Palmate leaves, on long, often reddish stalks, usually composed of 5 elliptical leaflets with serrate margins. Flowers small, polygamous, occurring toward the tips of stems in single or paired umbels that have long peduncles. Floral parts are in groups of 5, including the epigynous ovary surrounded by a nectar-secreting disc. Fruit, a drupe, contains the same number of kernels as carpels. Flower and fruit resemble those of ivy (*Hedera helix*) (*8*).

[1] A 33% ethanol extract of Radix Eleutherococci is listed as Extractum Radicis et Rhizomatis Eleutherococcus in the Russian Pharmacopoeia (*4*, *5*).

## Plant material of interest: dried roots and rhizomes

Roots from the unrelated plant *Periploca sepium* Bunge (Asclepiadaceae) (Chinese silk vine) have been surreptitiously used as a substitute for Radix Eleutherococci in commerce. To a lesser extent, roots from the related *Acanthopanax* species and *Kalopanax septemlobus* (Thunb.) Koidz. (Araliaceae) have also been so used (*9, 10*).

### General appearance

Roots: cylindrical, up to 0.5 cm in diameter, straight, occasionally branched, dark brown, smooth surface with bark adhering closely to the xylem. Rhizomes: up to 4 cm thick, pale brown, longitudinally wrinkled, showing root scars and traces of aerial stems; fracture somewhat fibrous; fractured surface pale yellow (*1*).

### Organoleptic properties

Odour: faint, aromatic; taste: bitter, acrid, persistent (*1*).

### Microscopic characteristics

Roots: rows (5–7) of brown cork cells; secondary phloem containing secretory canals in groups of 4 or 5, up to 20 μm in diameter, with brown contents; phloem fibres with thick, lignified walls occurring singly or in small groups; cluster crystals of calcium oxalate in phloem parenchyma; parenchymatous cells surrounding secretory cells and the medullary ray cells containing small starch grains; xylem of reticulate and bordered, pitted vessels. Rhizomes: similar to the roots except for larger secretory canals, up to 25 μm in diameter, and presence of parenchymatous pith containing starch grains (*1*).

### Powdered plant material

Yellowish; numerous groups of thick-walled, lignified fibres; fragments of reticulate and bordered, pitted vessels with a wide lumen; groups of secretory canals, up to 20 μm in diameter, with brown contents; parenchymatous cells containing cluster crystals of calcium oxalate 10–50 μm in diameter; small starch grains, rounded to slightly angular in outline, single or in groups of 2 or 3 (*3*).

## General identity tests

Macroscopic and microscopic examinations (*1–3*), thin-layer chromatography (*2, 3*) and high-performance liquid chromatography (*11–13*).

## Purity tests

### Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

### *Foreign organic matter*
Not more than 3% (3). Must be free of *Periploca sepium* and other foreign plant materials.

### *Total ash*
Not more than 6% (*1*).

### *Acid-insoluble ash*
Not more than 1.5% (*1*).

### *Water-soluble extractive*
Not less than 4% (*1*).

### *Alcohol-soluble extractive*
Not less than 6% using 75% ethanol (3).

### *Loss on drying*
Not more than 10% (3).

### *Pesticide residues*
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

### *Heavy metals*
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

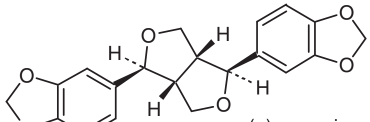
### *Radioactive residues*
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

### *Other purity tests*
Chemical tests to be established in accordance with national requirements.

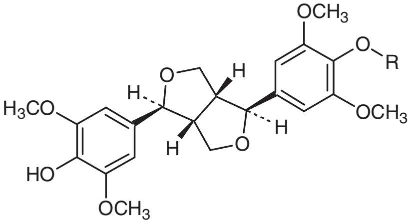
## Chemical assays
Several methods based on high-performance liquid chromatography are available for quantitative determination of syringaresinol-diglucoside (eleutheroside E) and syringin (eleutheroside B) (*11–13*).

## Major chemical constituents

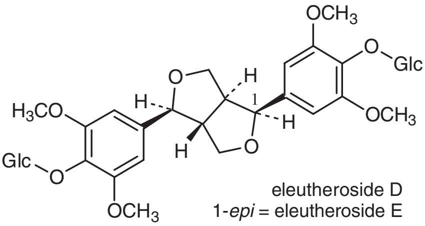
The constituents responsible for the characteristic biological effects of Radix Eleutherococci appear to be a complex mixture of phenylpropane derivatives of diverse structure, and various sugar polymers (*4, 6, 11*). The principal components of the former group are the lignans, (+)-sesamin (eleutheroside $B_4$), (+)-syringaresinol and its monoglucoside (eleutheroside $E_1$) and diglucoside (eleutherosides D and E); the simple phenylpropanes, syringenin and its monoglucoside (eleutheroside B); and the coumarins isofraxidin and its monoglucoside (eleutheroside $B_1$). An immunostimulant polysaccharide complex and a glycan series (eleutherans A–G) have also been isolated from the drug (*17*). β-Sitosterol and daucosterol (eleutheroside A) are the major sterols. Eleutheroside E has been found in all samples regardless of geographical origin, whereas eleutheroside B is present in all samples, except those from plants grown in the Democratic People's Republic of Korea (*11, 12*). The structures of the representative constituents are presented below.



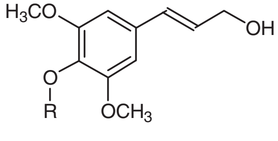
(+)-sesamin



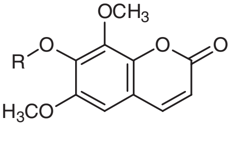
(+)-syringaresinol R = H
eleutheroside $E_1$ R = Glc



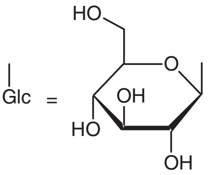
eleutheroside D
1-*epi* = eleutheroside E



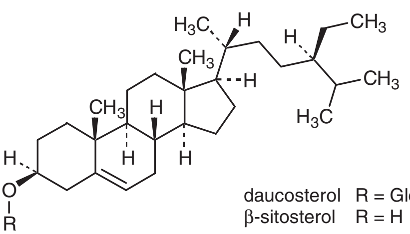
syringenin R = H
eleutheroside B R = Glc



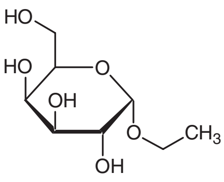
isofraxidin R = H
eleutheroside $B_1$ R = Glc



β-D-glucopyranosyl



daucosterol R = Glc
β-sitosterol R = H



eleutheroside C

## Medicinal uses

### *Uses supported by clinical data*

As a prophylactic and restorative tonic for enhancement of mental and physical capacities in cases of weakness, exhaustion and tiredness, and during convalescence (*4, 18–20*).

### *Uses described in pharmacopoeias and in traditional systems of medicine*

Treatment of rheumatoid arthritis, insomnia and dream-disturbed sleep (*2*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

As a carminative in the treatment of acute and chronic gastritis, as a diuretic, to treat impotence and to regulate blood pressure (*7*).

## Pharmacology

### *Experimental pharmacology*

#### Adaptogenic/antistress activity

The mechanism of the antistress or adaptogenic activities of Radix Eleutherococci appears to be threefold. Extracts of the roots have an adaptogenic effect that produces a non-specific increase in the body's defence against exogenous stress factors and noxious chemicals (*4, 21, 22*). The roots also stimulate the immune system, and promote an overall improvement in physical and mental performance (*4*).

Numerous in vivo studies have demonstrated the pharmacological activity of a 33% ethanol extract of the roots in a variety of animal models (*4, 23–29*). Most of these investigations were designed to analyse the adaptogenic response to a variety of adverse conditions (stress, immobilization or chemical challenge) (*4, 24, 25, 28, 30*). An increase in the resistance of rats to the toxic effects of noxious chemicals such as alloxan, cyclophosphan, ethymidine and benzo-tepa was observed after oral administration of a 33% ethanol extract of the roots (1–5 ml/kg body weight) (*24, 25, 28*). Intragastric administration of a 33% ethanol extract of the roots to mice (10 ml/kg body weight) decreased the toxicity of diethylglycolic acid, but did not reduce the severity of electroshock-induced convulsions (*31*). Administration of a 10% decoction of the roots to frogs' ventral lymph sac (0.1 ml) protected them against injection of lethal doses of cardiac glycosides (*32*). Intragastric administration of a 33% ethanol extract of the roots (1.0 ml/kg body weight) daily for 21–23 days increased the resistance of rats to the toxic effects of alloxan, but did not lower alloxan-induced hyperglycaemia (33). Intragastric administration of a freeze-dried extract of the roots (80 or 320 mg/kg body weight) daily for 3 days decreased blood glucose levels of mice by 35% and 60%, respectively, compared with placebo treat-

ment (*34*). Reduction of blood glucose levels may be due partially to enhanced synthesis of glycogen and high-energy phosphate compounds (*35*).

Investigations to elucidate the adaptogenic effect on the lymphatic system assessed the ability of root extracts to inhibit cortisone-induced weight decreases of the thymus and spleen in rats (*4*). Intraperitoneal administration of a 33% ethanol extract of the roots (1.0 ml/kg body weight) daily for 8 days prevented a decrease in spleen and thymus weight due to cortisone administration (*22*). A 33% ethanol root extract had normalizing effects on experimentally induced hypothermia when administered intragastrically to rats and mice (0.1 or 1.0 ml/kg body weight) daily for 12–14 days (*36*). Intragastric administration of a 33% ethanol extract of the roots to rats and mice normalized experimentally induced hypothermia, and acted as a sedative (*37*).

Intragastric administration of an aqueous extract of the roots to mice (500 mg/kg body weight) decreased stress-induced enlargement of the adrenal gland, normalized a decrease in rectal temperature due to chronic stress, and enhanced sexual behaviour (*26*). Intragastric administration of an aqueous extract of the roots (500 mg/kg body weight) daily for 15 days prolonged the swimming times of rats (*38*). Intragastric administration of an aqueous or butanol extract of the roots to rats (500 mg/kg body weight) suppressed gastric ulcer formation induced by stress (immersion in cold water) (*39*). Intragastric administration of an aqueous extract of the roots (500 mg/kg body weight) to rats suppressed the decrease in locomotor activity induced by exposure to light, indicating a reduction in the anxiety levels of the animals (*40*).

The antistress or adaptogenic effects of Radix Eleutherococci are produced through metabolic regulation of energy, nucleic acids and proteins of the tissues. Under stress, a β-lipoprotein–glucocorticoid complex is generated in the blood. This complex inhibits permeation of cell membranes by sugars and also inhibits hexokinase activity in vivo and in vitro (*4*). The root extracts increase the formation of glucose-6-phosphate, which in turn decreases the competition between the different pathways of its utilization. In animal tissues deficient in ATP, glucose-6-phosphate is oxidized via the pentose phosphate pathway, yielding substrates for the biosynthesis of nucleic acids and proteins (*4*). The constituents syringin (eleutheroside B) and (–)-syringaresinol-4,4′-*O*-β-D-diglucoside (eleutheroside E) are thought to be responsible for the adaptogenic activity (*21*). Intraperitoneal administration of total eleutherosides isolated from the roots to rats (5.0 mg/kg body weight) partially reversed the decrease in the levels of muscle ATP, glycogen, creatine phosphate, lactic acid and pyruvic acid induced by 2 hours of swimming. The same treatment also increased the work capacity of mice (*41*). Intraperitoneal administration of total eleutherosides to rats (15 mg/kg body weight), 1 hour prior to 15 minutes of forced swimming, delayed the inhibition of RNA polymerase. The same treatment also increased the activity of this enzyme during rest periods (*42*). Intragastric administration of a butanol extract of the roots to mice (170 mg/kg body weight, daily, 6 days a week for 6 weeks) enhanced the activities of oxidative enzymes and superoxide dismutase in skeletal muscle, resulting in improved aerobic metabolic

rates (*43*). Intragastric administration of an aqueous extract of the roots to mice (170 mg/kg body weight, daily for 9 weeks) increased the activity of succinate dehydrogenase and malate dehydrogenase in skeletal muscle (*44*).

Intraperitoneal administration of an aqueous root extract to mice (40–320 mg/kg body weight) increased sleeping times up to 228% compared to controls treated with hexobarbital, and decreased sleep latency when given in conjunction with hexobarbital (*45*).

Intraperitoneal administration of an aqueous extract of the roots to rats (3 mg/kg body weight) caused a significant increase in corticosterone levels 3 hours after injection, whereas adrenocorticotropic hormone levels remained unchanged (*40*). Intraperitoneal administration of a fluidextract of the roots (1.0 ml/kg body weight) increased anabolic activity in male rats (*46*). Oral administration of a glycoside fraction isolated from an ethanol root extract to rats (5.0 mg/kg body weight) increased the body weight and RNA content of the prostate and seminal vesicles, and inhibited atrophy of the prostate and seminal vesicles in castrated animals (*47*). A 30% ethanol extract of the roots was shown to bind in vitro to the estrogen receptor in rat uterus, and the glucocorticoid and mineralocorticoid receptors in rat kidney, but not to the androgen receptor in rat kidney (*48*).

**Antimicrobial activity**

Parenteral administration of a 33% ethanol extract of the roots (dose not specified) increased the resistance of mice and rabbits to listeriosis when administered for 15 days prior to infection (*49*, *50*). However, administration of the extract simultaneously with the bacteria increased the severity of the infection (*49*). Intragastric administration of the same extract (1 ml daily) for 15 days stimulated specific antiviral immunity in guinea-pigs and mice (*51*). A polysaccharide fraction of the roots (0.01 mg/ml) increased the activities of lymphokine-activated killer (LAK) cells and enhanced the activities of interleukin 2-stimulated LAK cells in vitro (*52*). A 95% ethanol extract of the roots (1 ml daily) increased phagocytosis of *Candida albicans* by human granulocytes and monocytes in vitro by 30–45% (*53*). Intraperitoneal administration of a polysaccharide fraction isolated from an aqueous root extract (10 mg/kg body weight) had immunostimulant activity in mice, as demonstrated by the colloidal carbon clearance test (*17*). A pyrogen-free polysaccharide fraction of the roots stimulated lymphocyte phagocytosis and T-cell-dependent functions of B-cells in vitro, as determined by plaque-forming cell stimulation assays and the production of anti-bovine serum albumin antibodies. Intraperitoneal administration of the same polysaccharide fraction to mice (100 mg/kg body weight daily for 7 days) significantly increased plaque-forming cell counts, anti-bovine serum albumin antibody levels and the phagocytic activity of lymphocytes (*54*). Intraperitoneal administration of a polysaccharide fraction of an aqueous extract of the roots to mice (125 mg/kg body weight) markedly increased the serum levels of anti-bovine serum albumin IgA and total anti-bovine serum albumin immunoglobulins, but not total IgA (*55*).

### Inhibition of platelet aggregation

A 100% methanol extract of the root inhibited ADP-induced platelet aggregation in blood samples from rats and humans in vitro (*56*).

## *Clinical pharmacology*

### Adaptogenic/antistress activity

Numerous clinical studies, designed to measure the adaptogenic effects of Radix Eleutherococci, were performed in Russia during the 1960s and 1970s (reviewed in Farnsworth et al., 1985 [*4*]). In 35 clinical trials without controls, involving over 2100 healthy subjects (4–1000 per study), oral administration of a 33% ethanol root extract (2.0–20.0 ml, daily for up to 60 days) improved physical and mental work performance under stress conditions, and reduced auditory disorders and the incidence of illness (*4*, *30*).

In another 35 clinical trials without controls, the effects of a 33% ethanol extract of the roots were assessed in 2200 patients (5–1200 per study) with various disorders, such as arteriosclerosis, acute pyelonephritis, diabetes, hypertension, hypotension, chronic bronchitis and rheumatic heart disease. Patients received 0.5–6.0 ml extract orally 1–3 times daily for up to eight courses of 35 days each, each course being separated by 2–3 weeks without treatment. The overall results were generally positive: for example, blood pressure was normalized, serum prothrombin and cholesterol levels were reduced, and overall well-being and physical work performance improved (*4*). It should be noted, however, that these trials lacked good methodology (for example, they used only a small number of patients, lacked proper controls and randomization, and were not double-blind).

A single-blind, placebo-controlled clinical trial in six baseball players assessed the effects of a 33% ethanol root extract on maximal work capacity. Three maximal work tests using a bicycle ergometer were performed on 3 consecutive days prior to treatment, and two tests were carried out after treatment with either 2 ml extract (containing 0.53 mg syringin (eleutheroside B) and 0.12 mg syringaresinol-4,-4′-*O*-β-diglucoside (identified here as eleutheroside D)) or placebo orally twice daily for 8 days. After each work test, maximal oxygen uptake, oxygen pulse, total work time and exhaustion time were measured. A significant improvement in all four parameters was observed in subjects treated with the extract ($P < 0.01$), including a 23.3% increase in total work time as compared with only a 7.5% increase following placebo treatment (*18*). A randomized, double-blind, placebo-controlled study measured the effect of an ethanol extract of the roots (standardized to contain 0.2% w/v syringin) on the immune system, using quantitative multiparameter flow cytometry with monoclonal antibodies directed against specific surface markers of human lymphocyte subsets to determine cellular immune status. Thirty-six healthy subjects were treated orally with either 10 ml extract or placebo three times daily for 4 weeks. Subjects treated with the extract had a significant increase in the total number of immunocompetent cells ($P < 0.0001$), including lymphocytes

(predominantly T-cells, T-helper/inducer cells and natural killer cells). A significant increase in activated T-cells was also observed ($P < 0.01$) (*19*). A randomized, double-blind, placebo-controlled study examined the effect of the crude drug on submaximal and maximal exercise performance. Twenty highly trained distance runners received either a 30–34% ethanol extract of the roots (3.4 ml) or placebo daily for 8 weeks, during which they completed five trials of both 10 minute and maximal treadmill tests. Heart rate, oxygen consumption, expired minute volume, ventilatory equivalent for oxygen, respiratory exchange ratio and rating of perceived exertion were measured during both tests. Serum lactate levels were analysed in blood samples. No significant differences were observed in any of the measured parameters between the placebo and treatment groups (*57*). A randomized, placebo-controlled, crossover study of 30 healthy volunteers compared the effects of Radix Eleutherococci, *Panax ginseng* and placebo on maximal oxygen uptake, using a bicycle ergometer. After 6 weeks of treatment, maximal oxygen uptake increased significantly only in subjects who had received *P. ginseng* (*58*). A comparative study assessed the ability of tinctures of Radix Eleutherococci and *Leuzea carthamoides* (containing eleutherosides and ecdysones, respectively) to decrease blood coagulation in highly trained athletes. Athletes treated with a 20-day course of the Radix Eleutherococci tincture showed a decrease in blood coagulation, and the activity of blood coagulation factors induced by intensive training (*59*).

## Contraindications

Radix Eleutherococci should not be used during pregnancy or lactation, or by patients with blood pressure in excess of 180/90 mmHg (24/12 kPa) (*4*). Radix Eleutherococci is also contraindicated in cases of known allergy to plants of the Araliaceae family.

## Warnings

No information available.

## Precautions

### *Drug interactions*

There is one case report of an increased level of serum digoxin due to the concomitant use of digoxin and Radix Eleutherococci (*60*). However, the identity of the plant material as *Eleutherococcus senticosus* was not established, and it is believed that it may have been *Periploca sepium*, which contains cardiac glycosides (*9*, *10*).

### *Carcinogenesis, mutagenesis, impairment of fertility*

No carcinogenicity was observed in rats (*61*). No mutagenic activities were observed in the *Salmonella*/microsome assay using *S. typhimurium* strains TA100

and TA98, in the mouse bone marrow micronucleus test, or in rats in vivo (*61*). Desmutagenic effects were observed in *Drosophila* (*62*, *63*).

### Pregnancy: teratogenic effects

No teratogenic effects were observed in the offspring of rats administered total eleutherosides intragastrically (10 mg/kg body weight) daily for 16 days, or in pregnant rats given 13.5 ml/kg body weight fluidextract of Radix Eleutherococci daily during days 6–15 of gestation (*64*, *65*). No teratogenic effects were observed in the offspring of sheep or mink when an ethanol extract of the roots was added to the diet (*4*). (See also Contraindications.)

### Pregnancy: non-teratogenic effects

See Contraindications.

### Nursing mothers

See Contraindications.

### Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions or paediatric use. Therefore, Radix Eleutherococci should not be used in children without medical supervision.

## Adverse reactions

A few cases of insomnia, arrhythmia (including tachycardia), extrasystole and hypertonia were reported in a clinical study involving 64 patients with atherosclerosis, who received a 33% ethanol extract of the crude drug at a dose of 4.5–6.0 ml daily for 6–8 cycles of treatment (lasting 25–35 days) (*66*). In another study of 55 patients with rheumatic heart lesions, two patients experienced hypertension, pericardial pain and palpitations, and pressure headaches after ingesting 3 ml of a 33% ethanol extract of the roots daily for 28 days (*67*). Insomnia has also been reported as a side-effect in other clinical trials (*4*). In one case report, neonatal androgenization was tentatively associated with the ingestion of Radix Eleutherococci tablets during pregnancy (*68*, *69*). However, analysis of the raw materials used in the preparation of the tablets indicated that they were probably from *Periploca sepium* (*70*). Furthermore, intragastric administration of either Radix Eleutherococci or *P. sepium* to rats (1.5 g/kg body weight) did not demonstrate any androgenization potential, indicating that the neonatal androgenization was probably not due to the plant material (*71*).

## Dosage forms

Powdered crude drug or extracts in capsules, tablets, teas, syrups, fluidextracts (*63*). Store in a well-closed container, protected from light (3).

## Posology

(Unless otherwise indicated)
Daily dosage: 2–3 g powdered crude drug or equivalent preparations (*20*).

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# Aetheroleum Eucalypti

## Definition

Aetheroleum Eucalypti is the essential oil obtained by steam distillation and rectification of the fresh leaves or terminal branchlets of *Eucalyptus globulus* Labill (Myrtaceae) or other *Eucalyptus* species rich in 1,8-cineole (*1–3*).

## Synonyms

*Eucalyptus cordata* Miq., *E. diversifolia* Miq., *E. gigantea* Dehnh., *E. glauca* D.C., *E. globulus* St Lag., *E. pulverulenta* Link (*4*).

## Selected vernacular names

Aceite de eucalipto, esencia de eucalipto, essence d'eucalyptus rectifiée, eucalipto essenza, eucalyptus oil, eucalyptus olie, Eucalyptusöl, huile essentielle d'eucalyptus, klei de eucalipt, minyak ekaliptus, oleo de eucalipto, Oleum eucalypti, tinh dâu Bach dan (*1–7*).

## Geographical distribution

Indigenous to Australia, cultivated in subtropical regions of the world including Africa, South America (e.g. Argentina, Brazil and Paraguay), Asia (e.g. China, India and Indonesia), southern Europe and the United States of America (*4*, *7–11*).

## Description

A large tree with smooth bark, very pale or ash-grey, up to 3–20 m high. Branchlets quadrangular, glaucous. Leaves of young trees and first leaves of young shoots opposite, sessile, oval-oblong, with a cordate base, farinaceous-glaucous; older leaves dangling, spirally arranged, lanceolate-falcate, up to 30 cm long. Flowers with very short pedicels, mostly umbellate, sometimes 2–3 in a fascicle. Calyx-tube double: outer tube drops early, smooth, inner tube semi-persistent and warty. Stamens about 1.5 cm long; fruit turbinate, angular, 2.0–2.5 cm in diameter (*12*, *13*).

## Plant material of interest: essential oil

### General appearance

A colourless or pale yellow liquid that darkens slightly on long storage (*1*, *2*).

### Organoleptic properties

Odour: aromatic, camphoric; taste: pungent, camphoric, followed by a sensation of cold (*1–3*).

### Microscopic characteristics

Not applicable.

### Powdered plant material

Not applicable.

## General identity tests

Thin-layer and gas chromatography (*1–3*).

## Purity tests

### Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

### Chemical

Refractive index: 1.458–1.470 (*1–3*); specific gravity: 0.906–0.925 (*2*); optical rotation: 0° to +10° (*2*); solubility in ethanol: soluble in 5 volumes of 70% ethanol (*2*, *5*). Methods to detect the presence of aldehyde and phellendrene are available (*2*).

### Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

### Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

### Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

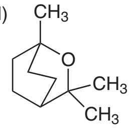
## Chemical assays

Contains not less than 70% (w/w) 1,8-cineole (also known as cineol, cineole or eucalyptol) (*1, 2*). Quantitative analysis according to the method described for 1,8-cineole (*1–3*).

## Major chemical constituents

The major constituent is 1,8-cineole (54–95%). In addition, there are moderate amounts of α-pinene (2.6%), *p*-cymene (2.7%), aromadendrene, cuminaldehyde, globulol and pinocarveol (*11, 13*). The structure of 1,8-cineole is presented below.

1,8-cineole (eucalyptol)




## Medicinal uses

### *Uses supported by clinical data*

None.

### *Uses described in pharmacopoeias and in traditional systems of medicine*

Symptomatic treatment of catarrh and coughs (*17, 18*). As a component of certain dental root canal sealers; topically as a rubefacient for treatment of rheumatic complaints (*18, 19*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of cystitis, diabetes, gastritis, kidney disease (unspecified), neuralgia, laryngitis, leukorrhoea, malaria, pimples, ringworm, sinusitis, wounds, ulcers of the skin, urethritis and vaginitis (*4, 6*).

## Pharmacology

### *Experimental pharmacology*

#### Antimicrobial activity

Aetheroleum Eucalypti inhibited the growth in vitro of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Enterococcus faecalis* and *Escherichia coli* (*20–25*), but not of *Bacillus cereus*, *Penicillium cyclopium* or *Aspergillus aegyptiacus* (*22, 25*). Intramuscular injection of the essential oil (500 mg/kg body weight) inhibited the growth of *Mycobacterium tuberculosis* in guinea-pigs, and enhanced the efficacy of streptomycin and isoniazid (*26*).

### Anti-inflammatory activity

The essential oil inhibited prostaglandin biosynthesis in vitro at a concentration of 37 µmol/l (*27*).

### Respiratory tract effects

Intragastric administration of the essential oil increased respiratory tract secretions in cats (100 mg/kg body weight), guinea-pigs (50 mg/kg body weight), rabbits (100 mg/kg body weight) and rats (100 mg/kg body weight) (*28*). Administration of non-lethal doses of the essential oil by steam inhalation to urethane-treated rabbits did not enhance the output of respiratory tract fluid (*29*).

### Antitussive effects

The antitussive effect of the essential oil was compared to that of codeine in guinea-pigs in which coughs were induced by mechanical stimulation. Inhalation of the essential oil (5% emulsified in normal saline) had a significant antitussive effect relative to codeine (15 mg/kg body weight) of 0.68 ($P < 0.05$). When the essential oil was administered by intraperitoneal injection (50 mg/kg body weight), the antitussive effect relative to codeine was 0.57, which was also significant ($P < 0.001$) (*30*).

## *Clinical pharmacology*

### Nasal decongestant activity

A clinical trial without controls assessed the effects of Aetheroleum Eucalypti as a nasal decongestant in 31 healthy volunteers. Inhalation of the essential oil (10 ml) over a period of 5 minutes had no effect on nasal resistance to airflow. However, the oil had a stimulant or sensitizing effect on nasal cold receptors, and the majority of subjects reported a sensation of increased airflow (*31*). A single-blind, parallel clinical trial assessed the efficacy of vaporized essential oil, camphor, menthol or steam in reducing nasal congestion in 234 patients with acute respiratory tract infections. The essential oil was significantly more effective in reducing nasal congestion only during the first hour following treatment ($P < 0.02$) (*32*). In other clinical studies of patients with acute common colds, no significant differences in nasal decongestant activity were reported between the essential oil (1.3%) in petrolatum and a petrolatum placebo (*32*).

### Analgesic activity

A randomized, double-blind, placebo-controlled, crossover study assessed the efficacy of a combination product of the essential oil (eucalyptus oil) and Aetheroleum Menthae Piperitae (peppermint oil) for headache relief in 32 patients. Five different preparations were used (all in 90% ethanol, to a final weight of 100 g): 10 g peppermint oil and 5 g eucalyptus oil; 10 g peppermint oil and traces of eucalyptus oil; traces of peppermint oil and 5 g eucalyptus oil; traces of both peppermint oil and eucalyptus oil; or a placebo. The test

preparations or placebo were applied topically to large areas of the forehead and temples, and the effects on neurophysiological, psychological and experimental algesimetric parameters were measured. All test preparations improved cognitive performance, and induced muscle and mental relaxation compared to the placebo, but had no effect on sensitivity to headache (*33*).

## Contraindications

Preparations of Aetheroleum Eucalypti should not be administered internally to children (*34*), or patients with inflammation of the gastrointestinal tract, gall bladder disease or impaired liver function (*4*, *17*, *34*). Aetheroleum Eucalypti should not be taken internally during pregnancy (*35*), see Precautions.

## Warnings

Aetheroleum Eucalypti preparations should not be applied to the face, especially the nose, of infants or young children (*17*). Keep out of reach of children.

## Precautions

### *General*

Oily vehicles for the essential oil are unsuitable for use in nasal sprays as the vehicle inhibits ciliary movement and may cause lipid pneumonia (*19*).

### *Drug interactions*

Although no published drug interactions were found, a number of animal studies indicate possible concern that the essential oil may induce liver enzymes involved in drug metabolism. Therefore, the effects of other drugs may be decreased following concomitant administration (*17*, *36*).

### *Carcinogenesis, mutagenesis, impairment of fertility*

The essential oil was a weak promoter of papilloma formation by 9, 10-dimethyl-12-benzanthracene in mice. However, the development of tumours in mice after intragastric administration of 8 or 32 mg 1,8-cineole per kg body weight daily for 80 weeks was similar to that in mice treated with vehicle controls (*37*).

### *Pregnancy: teratogenic effects*

The essential oil was not teratogenic when administered subcutaneously to pregnant mice (135 mg/kg body weight) daily on days 6–15 of gestation (*38*).

### *Pregnancy: non-teratogenic effects*

Eucalyptol (500 mg/kg body weight, administered subcutaneously) has been reported to penetrate the placenta in rodents and reach concentrations in the

fetal blood which are sufficient to stimulate hepatic enzyme activity (*39*). Therefore, Aetheroleum Eucalypti should not be taken internally during pregnancy (*35*).

### *Paediatric use*

See Contraindications and Warnings.

### *Other precautions*

No information available on precautions concerning drug and laboratory test interactions or nursing mothers. Therefore, Aetheroleum Eucalypti should not be administered during lactation without medical supervision.

## Adverse reactions

Topical applications of Aetheroleum Eucalypti are generally non-irritating, non-sensitizing and non-phototoxic (*40*). However, one case of systemic toxicity in a 6-year-old girl (*41*), and several cases of urticaria, contact dermatitis and skin irritation (*42*) have been reported.

Between 1981 and 1992, the clinical effects of poisoning were observed in 59% of 109 children after accidental ingestion of the essential oil (2–10 ml) (*43, 44*). The symptoms included depression of conscious state (28% of cases), drowsiness (25% of cases) and unconsciousness (3% of cases), and were dose-dependent (*43*). Other reported symptoms included epigastric burning, nausea, vomiting, dizziness, muscular weakness, miosis, a feeling of suffocation, cyanosis, delirium and convulsions (*8, 18, 45*). Allergic reactions have been reported after ingestion of 20 lozenges containing the essential oil (*46*).

Between 1889 and 1922, 17 cases of fatal poisoning due to ingestion of the essential oil were reported (*36*). A dose of as little as 3.5 ml was fatal (*47*). However, these data are old and the purity of the oil used is unknown.

## Dosage forms

Essential oil in solid, semisolid or liquid preparations (*1*) and galenical preparations (*17*). Store in a well-filled, tightly closed container, protected from heat and light (*1, 2*).

## Posology

(Unless otherwise indicated)

#### Internal use

Daily dosage: 0.3–0.6 ml essential oil or equivalent preparations (*17*). Capsules: 1 capsule of 100–200 mg, 2–5 times daily (*48, 49*). Lozenges: 1 lozenge of 0.2–15.0 mg dissolved slowly in the mouth, every 30–60 minutes (*32*). Mouth-

wash: 20 ml of a 0.91 mg/ml solution, gargled twice daily (*32*). Inhalation: 12 drops/150 ml boiling water (*49*).

### External use

Daily dosage: several drops (*17*) or 30 ml essential oil in 500 ml lukewarm water (*35*) rubbed into the skin for local application; 5–20% essential oil in liquid and semisolid preparations; 5–10% in hydroalcoholic preparations.

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# Folium Eucalypti

## Definition

Folium Eucalypti consists of the dried leaves of *Eucalyptus globulus* Labill (Myrtaceae) (*1–3*).

## Synonyms

*Eucalyptus cordata* Miq., *E. diversifolia* Miq., *E. gigantea* Dehnh., *E. glauca* D.C., *E. globulus* St Lag., *E. pulverulenta* Link (*4*).

## Selected vernacular names

Alcanfor, arbre à la fièvre, Australian fever tree, bach dan xanh, Blaugummibaum, bluegum tree, calibtus, calipso, daun ekaliptus, eucalipus, eucalypto, eucalyptus, Eucalyptusblätter, feuilles d'eucalyptus, fevertree, Fieberbaum, Fieberhilbaum, gigante, gommier bleu, gommier bleu de Tasmania, gum tree, iron bark tree, kalatus, kaphur, khuynh diep, mtiulaya, nkwu-ishi, oykaliptus, Tasmanian bluegum, yukari (*1, 4–8*).

## Geographical distribution

Indigenous to Australia, cultivated in subtropical regions of the world including Africa, South America (e.g. Argentina, Brazil and Paraguay), Asia (e.g. China, India and Indonesia), southern Europe and the United States of America (*1, 4, 6, 8–10*).

## Description

A large tree with smooth bark, very pale or ash-grey, up to 3–20 m high. Branchlets quadrangular, glaucous. Leaves of young trees and first leaves of young shoots opposite, sessile, oval-oblong, with a cordate base, farinaceous-glaucous; older leaves dangling, spirally arranged, lanceolate-falcate, up to 30 cm long. Flowers with very short pedicels, mostly umbellate, sometimes 2–3 in a fascicle. Calyx tube double: outer tube drops early, smooth; inner tube semipersistent and warty. Stamens about 1.5 cm long. Fruit turbinate, angular, 2.0–2.5 cm in diameter (*11, 12*).

## Plant material of interest: dried leaves

### *General appearance*

Leaf lanceolate-falcate, bifacial, 8–30 cm long, 2–7 cm wide; petiole twisted, strongly wrinkled, 2–3 cm, occasionally 5 cm, in length; apex, when present, acute or acuminate; base unequal, obtuse or somewhat rounded, margin uneven, revolute; ventral and dorsal surfaces greyish-green to pale yellowish-green, coriaceous, glaucous, glabrous, glandular-punctate, with numerous small, rounded, brown dots of cork; venation pinnate-reticulate, veins of the first order running to a short distance from margin where they are anastomosed and form a vein nearly parallel with the margin (*1–3*, *8*).

### *Organoleptic properties*

Odour: aromatic, camphoric; taste: aromatic, pungent, bitter (*1*, *3*, *8*).

### *Microscopic characteristics*

Upper and lower epidermis composed of clear, polygonal cells with thick cutinized outer walls; both layers possess sunken stomata. Chlorenchyma differentiated into 2 palisade regions: both regions composed of 3–4 (usually 4) rows of cells which face each epidermis; in each region large, subglobular internal glands occur, lined with secretory epithelium and containing yellow oil. Parenchyma spongy, a narrow zone of loosely arranged cells between the 2 palisade regions; its cells contain rosette aggregates or monoclinic prisms of calcium oxalate crystals. Fibrovascular bundles throughout the spongy parenchyma; in midrib and petiole, interrupted arc of slightly lignified pericyclic fibres occurs just outside these bundles (*8*).

### *Powdered plant material*

Greyish-green; fragments of chlorenchyma with numerous embedded, broken, yellow, schizogenous oil glands; calcium oxalate crystals in rosette aggregates or monoclinic prisms; fragments of epidermis with polygonal cells having very thick cuticle, numerous anomocytic stomata of more than 80 μm in diameter, fragments of sclerenchyma fibres; fragments of cork, tracheids, vessels and fibres (*1*, *3*, *8*).

## General identity tests

Macroscopic and microscopic examinations, microchemical analysis and thin-layer chromatography for 1,8-cineole (*1–3*, *8*, *13*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

### Foreign organic matter

Not more than 1% fruits, and not more than 2% stems and other foreign matter (*1–3*).

### Total ash

Not more than 6% (*2, 3*).

### Acid-insoluble ash

Not more than 0.2% (*8*).

### Loss on drying

Not more than 10% (*3*).

### Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

### Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

### Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

### Other purity tests

Chemical, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

## Chemical assays

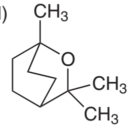
Contains not less than 2% (v/w) essential oil, consisting of not less than 70% (w/w) 1,8-cineole (also known as cineol, cineole or eucalyptol) (*1, 3*). A thin-layer chromatography method is available for qualitative determination, using 1,8-cineole as a reference standard (*3*).

## Major chemical constituents

Dried leaves contain 1–3% (v/w) essential oil (fresh leaves contain 0.4–1.6%), the major constituent of which is 1,8-cineole (54–95%). In addition, there are moderate amounts of other monoterpenes, including α-pinene (2.6%),

*p*-cymene (2.7%), aromadendrene, cuminaldehyde, globulol and pinocarveol. Gas chromatography and gas chromatography–mass spectroscopy of the oil indicated the presence of more than 70 components, 48 of which were identified. The concentration of α-terpeneol was estimated to be 28% (*17*). The leaves are rich in tannins and ellagitannins, and also contain 2–4% triterpenes (ursolic acid derivatives), a series of phloroglucinol-sesquiterpene-coupled derivatives (macrocarpals B, C, D, E, H, I and J) and flavonoids (rutin, quercetin, quercitrin and hyperoside) (*5, 7, 10, 12, 17–19*). The structure of the major monoterpene, 1,8-cineole, is presented below.

1,8-cineole (eucalyptol)




# Medicinal uses

## *Uses supported by clinical data*

None.

## *Uses described in pharmacopoeias and in traditional systems of medicine*

As an expectorant for symptomatic treatment of mild inflammation of the respiratory tract and bronchitis (*20*). Also for symptomatic treatment of asthma, fever and inflammation of the throat (*1*).

## *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of cystitis, diabetes, gastritis, kidney disease (unspecified), laryngitis, leukorrhoea, malaria, pimples, ringworm, wounds, ulcers of the skin, urethritis and vaginitis (*5*).

# Pharmacology

## *Experimental pharmacology*

### Antibacterial and antifungal activity

An ethanol–water extract of Folium Eucalypti inhibited the growth in vitro of *Staphylococcus aureus* at a concentration of 25 μg/ml (*21*). An aqueous leaf extract inhibited the growth in vitro of *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Enterococcus faecalis* (MIC 0.07–1.30 mg/ml) (*22*). A methanol extract of the leaves inhibited the growth in vitro of *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* (MIC 1.25–10.00 mg/ml) (*23*). A

fluidextract of the leaves inhibited the growth in vitro of *Mycobacterium tuberculosis* (MIC 6.25 mg/ml) (*24*). A methanol–water extract of the leaves inhibited the growth in vitro of *Candida albicans* (*25*).

#### Antiviral activity

An aqueous leaf extract inhibited the replication of influenza virus $A_2$ (Mannheim 57), vaccinia virus and herpes simplex virus type 2 in vitro at a concentration of 0.1% (*26*).

#### Antimalarial activity

Intragastric administration of a hexane leaf extract to mice (100 mg/kg body weight) did not inhibit the growth of *Plasmodium berghei* (*27*). Furthermore, administration of an aqueous (3.48 g/kg body weight) or chloroform (264 mg/kg body weight) leaf extract to chickens by gastric lavage did not inhibit the growth of *P. gallinaceum* (*28*). An ethanol–water extract of the leaves inhibited the growth in vitro of *P. falciparum* at a concentration of 75 µg/ml (*21*).

#### Antidiabetes activity

A hot aqueous extract of the leaves suppressed streptozocin-induced hyperglycaemia in mice when added to the diet (6.25%) and drinking-water (0.25%). The same extract did not stimulate insulin production by the pancreas (*29*). However, intragastric administration of aqueous or ethanol extracts of the leaves at a dose of 1 g/kg body weight did not suppress alloxan-induced hyperglycaemia in mice and rabbits (*30*, *31*).

### *Clinical pharmacology*

None.

## Contraindications

Preparations of Folium Eucalypti should not be administered internally to children or patients with inflammation of the gastrointestinal tract, gall bladder disease or impaired liver function (*4*, *20*).

## Warnings

Folium Eucalypti preparations should not be applied to the face, especially the nose, of infants or young children (*20*). Keep out of reach of children.

## Precautions

### *Drug interactions*

Although no published drug interactions were found, a number of animal studies indicate possible concern that the leaf essential oil may induce liver

enzymes involved in drug metabolism. Therefore, the effects of other drugs may be decreased following concomitant administration (*20*, *32* ).

### *Carcinogenesis, mutagenesis, impairment of fertility*

A tincture of the leaves was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA100 and TA98 (*33*).

### *Pregnancy: teratogenic effects*

The leaf essential oil was not teratogenic when administered subcutaneously to pregnant mice (135 mg/kg body weight) daily on days 6–15 of gestation (*34*).

### *Pregnancy: non-teratogenic effects*

Eucalyptol (500 mg/kg body weight, administered subcutaneously) has been reported to penetrate the placenta in rodents, and reach concentrations in the fetal blood which are sufficient to stimulate hepatic enzyme activity (*35*). Therefore, Folium Eucalypti should not be administered during pregnancy without medical supervision.

### *Paediatric use*

See Contraindications and Warnings.

### *Other precautions*

No information available on general precautions or precautions concerning drug and laboratory test interactions or nursing mothers. Therefore, Folium Eucalypti should not be used during lactation without medical supervision.

## Adverse reactions

Excessive ingestion of Folium Eucalypti can cause nausea, vomiting and diarrhoea (*20*). Several cases of urticaria, contact dermatitis and skin irritation have been reported after therapeutic doses (*36*).

## Dosage forms

Crude drug (*1*, *20*). Store in a tightly closed container, protected from light (*3*).

## Posology

(Unless otherwise indicated)

Daily dosage: 4–6 g crude drug or equivalent preparations. Infusion: pour 150 ml of hot water over a half teaspoon of the leaves, allow them to stand for 10 minutes, then remove the leaves with a strainer (*10*, *20*). One cup (240 ml) of the freshly prepared infusion is drunk slowly three times daily. The vapour of the hot infusion is inhaled deeply (*10*).

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# Cortex Frangulae

## Definition

Cortex Frangulae consists of the dried bark of the stem and branches of *Rhamnus frangula* L. (Rhamnaceae) (*1–3*).

## Synonyms

*Frangula alnus* Mill., *F. frangula* (L.) Karst., *F. vulgaris* Borgh., *Rhamnus alnus* Mill., *R. korolkowii* Hort. Rehd., *R. nemoralis* Salisb., *R. pentapetala* Gilib. Ortega (*1*, *2*, *4*).

## Selected vernacular names

Alder buck, alder buckthorn, alder dogwood, alno nero, alqueshra almoqadassa, amieiro preto, Amselbaum, arrow-wood, awsag aswad, bird cherry, black alder, black alder bark, black dog wood, bois à poudre, bois noir, bourdaine, Brechwegdorn, buckthorn, buckthorn bark, casca de amiero, corteccia di frangola, cortex frangulae, Cortex rhamni frangulae, corteza de arraclau, corteza de frangula, dog wood, écorce d'aune noir, écorce de bourdaine, écorce de frangule, Faulbaum, frangola, frangula, Gelbholzrinde, Glatter Wegdorn, glossy buckthorn, Grindholz, krusinnik, kulit frangula, kutyabengekéreg, Pulverholz, Pulverholzrinde, purging buckthorn, quishrul awsagel aswad, rhamnusbast, Schwarzholz, seyah-tusseh, shagrat hhabb esh shung, siâh-touseh, Spillbaum, sporkenhoutbast, vuilboombast, Zapfenholz, Zweckenholz (*1*, *4–7*).

## Geographical distribution

Indigenous to Mediterranean countries and temperate regions of Africa, western Asia and Europe (*1*, *8*).

## Description

A shrub, 3–5 m high with non-thorny stalks and dark-red to purplish-blue young branches spotted with greenish lenticels. Leaves alternate and ovate, entire or slightly sinuate along the margin, and have parallel secondary veins which curve as they meet the edge of the blade. Flowers small, greenish-white, hermaphrodite, pentamerous, arranged in axillary clusters of

2–3. Fruit a drupe, red at first, then black at maturity, with 2 or 3 seeds (*1*, *9*, *10*).

## Plant material of interest: dried bark

The fresh bark contains free anthrones and must be stored for at least 1 year or artificially aged by heat or aeration before therapeutic use (*1*, *11*, *12*).

### *General appearance*

Single or double quills, rarely in channelled pieces; usually 15 cm long, 0.5–2 cm wide and extremely thin (not more than 2 mm thick). Outer surface greyish-brown or purplish-black, wrinkled, with numerous transversely elongated whitish lenticels; sometimes bearing patches of foliaceous lichen, with small black apothecia; when gently scratched, crimson colour of inner layers of cork becomes evident. Inner surface reddish-yellow to dark brown; fine longitudinal striations, becoming red when moistened with dilute solutions of alkali (Bornträger's test). Fracture, short in the outer part and slightly fibrous in the inner part (*1*, *2*).

### *Organoleptic properties*

Odour: characteristic; taste: sweetish then slightly bitter and astringent; mucilaginous (*1*, *8*).

### *Microscopic characteristics*

Cortex yellowish-brown, consisting of thin-walled parenchyma, containing scattered cluster crystals of calcium oxalate and few small starch grains, and showing large cells filled with mucilage and few groups of slightly lignified fibres, each up to 40 μm wide. Phloem yellowish-brown, traversed by numerous, somewhat wavy medullary rays, 1–3 cells wide and 10–25 cells high, and showing numerous tangential groups of strongly lignified bast fibres, accompanied by prismatic crystals of calcium oxalate, forming a crystal sheath around each group; individual fibres 12–24 μm in diameter (*1*).

### *Powdered plant material*

Yellowish-brown. Fragments of reddish-brown cork; fragments of groups of lignified bast fibres, accompanied by a calcium oxalate crystal sheath; occasional fragments of slightly lignified fibres; fragments showing cells of medullary rays, with yellow contents which turn red with solutions of alkali or with sodium hypochlorite solution; cluster crystals of calcium oxalate, 10–25 μm in diameter; prismatic crystals of calcium oxalate, 7–15 μm long; few starch grains 3–10 μm in diameter; sclereid cells absent (*1*, *2*).

## General identity tests

Macroscopic, microscopic and microchemical (Bornträger's test) examinations and thin-layer chromatography for characteristic hydroxyanthracene glycosides (*1*, *2*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

### *Foreign matter*

Not more than 1% (*2*).

### *Total ash*

Not more than 6% (*2*).

### *Acid-insoluble ash*

Not more than 2% (*1*).

### *Loss on drying*

Not more than 10% (*2*).

### *Pesticide residues*

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

### *Heavy metals*

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

### *Radioactive residues*

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

### *Other purity tests*

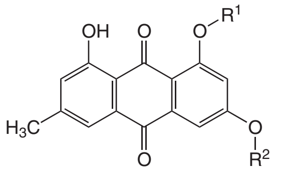
Chemical, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

## Chemical assays

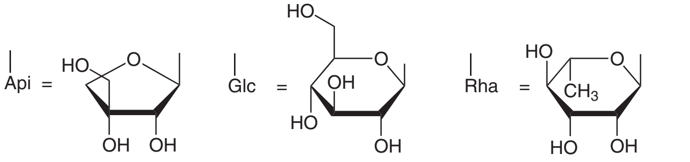
Contains not less than 7.0% of glucofrangulins, calculated as glucofrangulin A, determined by spectrophotometry at 515 nm (*2*). The high-performance liquid chromatography method reported for quantitative analysis of cascarosides (*16*) can also be considered.

## Major chemical constituents

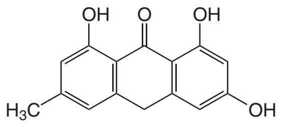
The active constituents are hydroxyanthraquinone glycosides (3–8%) consisting of monoglycosides and diglycosides of frangula emodin, with the diglycosides, glucofrangulins A and B, being the major compounds. The major monoglucosides are frangulins A and B (*17*). Other anthranoid derivatives present include emodin anthrone-6-*O*-rhamnoside (franguloside), as well as physcion and chrysophanol in glycosidic and aglycone forms (*17*, *18*). In the fresh bark, anthraquinones are not present, but exist as their reduced anthrone and dianthrone glycosides, which are converted by oxidation during drying and storage, or by accelerated heat and air treatment (*4*, *6*, *8*, *9*, *17*). The structures of the major anthraquinone glycosides, free anthraquinones and frangula emodin anthrone are presented below.




| | $R^1$ | $R^2$ |
|---|---|---|
| frangula emodin | H | H |
| frangulin A | H | Rha |
| glucofrangulin A | Glc | Rha |
| frangulin B | H | Api |
| glucofrangulin B | Glc | Api |




D-*apio*-β-D-furanosyl β-D-glucopyranosyl 6-deoxy-α-L-mannopyranosyl




frangula emodin anthrone

## Medicinal uses

### Uses supported by clinical data

Short-term treatment of occasional constipation (*1*, *9–11*). As a single dose, for total intestinal evacuation before X-rays and other diagnostic examinations when electrolyte solutions alone are insufficient for adequate evacuation or the use of electrolyte solutions is not possible (*11*).

### Uses described in pharmacopoeias and in traditional systems of medicine

As a cathartic (*1*).

### Uses described in folk medicine, not supported by experimental or clinical data

Internally for treatment of diabetes and externally for skin irritations (*6*).

### Experimental pharmacology

#### Laxative effects

The pharmacological effects of Cortex Frangulae are associated with the hydroxyanthraquinone glycosides, glucofrangulins A and B, and frangulins A and B (*17*). After oral administration of Cortex Frangulae, the hydroxyanthracene glycosides are not absorbed in the upper intestine, but are hydrolysed in the colon by intestinal bacteria to form the pharmacologically active metabolites. These metabolites are partially absorbed in the colon and act as a stimulant and irritant to the gastrointestinal tract, as does senna (*11*, *18*, *19*, *20*). The mechanism of action, similar to that of senna, is twofold. Firstly, there is stimulation of colonic motility, resulting in augmented propulsion, and accelerated colonic transit (which reduces fluid absorption from the faecal mass). Secondly, there is an increase in paracellular permeability across the colonic mucosa, probably due to inhibition of sodium/potassium-transporting adenosine triphosphatase or inhibition of chloride channels (*18*, *21*). The increased permeability results in increased water content in the colon (*11*, *21*).

The laxative effect of Cortex Frangulae is not generally observed until 6–8 hours after oral administration. Hydroxyanthracene glycosides are excreted predominantly in the faeces but are also excreted to some extent in urine, producing an orange colour; anthrones and anthranols will also pass into breast milk (*18*).

#### Toxicity and overdose

As with other anthraquinone laxatives, the major symptoms of overdose are gripes and severe diarrhoea with consequent loss of fluid and electrolytes (*22*). Treatment of overdose should be supportive with generous amounts of fluid. Electrolyte levels should be monitored, particularly those of potassium. This is especially important in children and the elderly (*22*).

## Clinical pharmacology

None.

## Contraindications

Cortex Frangulae should not be administered to patients with intestinal obstruction and stenosis, atony, inflammatory diseases of the colon (such as ulcerative colitis, irritable bowel syndrome, Crohn disease), appendicitis, severe dehydration with water and electrolyte depletion, or chronic constipation (*9, 19, 23*). As with other stimulant laxatives, Cortex Frangulae is contraindicated in patients with cramps, colic, haemorrhoids, nephritis, or any undiagnosed abdominal symptoms such as abdominal pain, nausea or vomiting (*22*). Cortex Frangulae and other anthranoid laxatives are contraindicated during pregnancy because of their pronounced action on the large intestine and the lack of data on their toxicology (*24, 25*). As anthranoid metabolites may appear in breast milk, Cortex Frangulae should not be used during lactation, since there are insufficient data to assess the potential for pharmacological effects in the breastfed infant (*25*). Use of Cortex Frangulae for children under the age of 12 years is contraindicated (*11*).

## Warnings

Cortex Frangulae should only be used if no effect can be obtained through a change of diet or by the use of bulk-forming laxatives. Patients should also be warned that certain constituents of the bark are excreted by the kidney and may colour the urine orange, which is harmless. Cortex Frangulae and other stimulant laxatives should not be used by patients with abdominal pain, nausea or vomiting. The use of stimulant laxatives for longer than 2 weeks requires medical supervision. Rectal bleeding or failure to have a bowel movement after taking a laxative may indicate a serious condition. Chronic use may result in aggravation of constipation with laxative dependence and need for increased dosages, and disturbances of water and electrolyte balance (e.g. hypokalaemia). Chronic use may also lead to colonic dysfunction (atonicity) and melanotic pigmentation of the colonic mucosa (pseudomelanosis coli), which is harmless (*22*). Laxative abuse resulting in diarrhoea and consequent fluid and electrolyte losses (mainly of potassium) may cause albuminuria, haematuria, and cardiac and neuromuscular dysfunction. Neuromuscular dysfunction may arise particularly in the case of concomitant use of cardiotonic glycosides (e.g. digoxin, digitalis and strophanthin), diuretics, corticosteroids or liquorice root (*22*).

## Precautions

### *General*

Cortex Frangulae and other laxatives containing anthraquinone glycosides should not be used continuously for longer than 1–2 weeks, because of the possibility of electrolyte imbalance (*22*).

### Drug interactions

Increased intestinal transit time may result in reduced absorption of orally administered drugs (*26*). Electrolyte imbalances, such as hypokalaemia, may potentiate the effects of cardiotonic glycosides (e.g. digoxin, digitalis and strophanthus). Hypokalaemia resulting from long-term laxative abuse can also potentiate the effects of antiarrhythmic drugs (e.g. quinidine) that change sinus rhythm by affecting potassium channels. Hypokalaemia caused by drugs such as thiazide diuretics, adrenocorticosteroids or liquorice root may be exacerbated, and imbalance of other electrolytes may be aggravated (*11*).

### Drug and laboratory test interactions

Anthranoid metabolites may not be detectable in faeces or urine by standard methods. Thus faecal excretion measurements may not be reliable (*26*). Urinary excretion of certain anthranoid metabolites may cause discoloration of the urine which is not clinically relevant, but may cause false positives in urinary urobilinogen tests and in estrogen measurements using the Kober procedure (*27*).

### Carcinogenesis, mutagenesis, impairment of fertility

Although chronic use of anthranoid-containing laxatives has been hypothesized to play a role in colorectal cancer, no causal relationship has been demonstrated (*28–31*).

Various Cortex Frangulae extracts have been shown to be genotoxic in several in vitro systems, resulting in bacterial mutation, and chromosomal aberration and DNA-repair defects in mammalian cells. However, no mutagenicity was observed in a gene mutation assay in mammalian cells (*23*). Frangula emodin was mutagenic in the *Salmonella*/microsome assay with *S. typhimurium* strain TA1537 only, but gave inconsistent results in gene mutation assays in mammalian cells. Frangula emodin was also a strong inducer of unscheduled DNA synthesis in primary rat hepatocytes, but gave negative results in the sister chromatid exchange assay (*18*, *23*, *32*, *33*).

### Pregnancy: teratogenic effects

The teratogenic effects of Cortex Frangulae have not been evaluated. (See also Contraindications.)

### Pregnancy: non-teratogenic effects

See Contraindications.

### Nursing mothers

See Contraindications.

### Paediatric use

See Contraindications.

## Adverse reactions

Single doses of Cortex Frangulae may result in cramp-like discomfort of the gastrointestinal tract, which may require a reduction of dosage (*11*). Overdose can lead to colicky abdominal spasms and pain, as well as the formation of thin, watery stools.

Long-term laxative abuse may lead to electrolyte imbalance (hypokalaemia and hypocalcaemia being the most important), metabolic acidosis, malabsorption of nutrients, weight loss, albuminuria and haematuria (*34, 35*). Weakness and orthostatic hypotension may be exacerbated in elderly patients when stimulant laxatives are repeatedly used. Secondary aldosteronism may occur due to renal tubular damage after prolonged use. Steatorrhoea and protein-losing gastroenteropathy with hypoalbuminaemia have also been reported in laxative abuse (*36*). Pseudomelanosis coli has been observed in individuals taking anthraquinone laxatives for extended time periods (*22, 35*). The pigmentation is harmless and usually reversible within 4–12 months after the drug is discontinued (*35*). Conflicting data exist on other toxic effects after long-term use such as damage to the autonomous nervous system of the colon (*35, 37*). In incontinent patients using anthranoid laxatives, prolonged exposure of the skin to faeces may cause skin damage (*38*).

Use of the fresh bark of *Rhamnus frangula* may cause severe vomiting, with possible abdominal spasms (*18*).

## Dosage forms

Finely cut and powdered crude drug, powder, dried extract, liquid and solid preparations (*8*). Store in a tightly closed, light-resistant container for a maximum of 3 years (*1, 2*).

## Posology

(Unless otherwise indicated)

The correct dosage for the treatment of occasional constipation is the smallest dosage necessary to maintain a soft stool. Daily dosage: 0.5–2.5 g crude drug taken directly or in a decoction; 0.5–2.5 ml 25% ethanol extract (*18*); all preparations standardized to contain 20–30 mg hydroxyanthracene derivatives calculated as glucofrangulin A (*11*); taken at bedtime, or in two divided doses, one in the morning and one at bedtime.

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# Folium et Cortex Hamamelidis

## Definition

Folium et Cortex Hamamelidis consists of the dried or fresh leaves and/or the dried bark of *Hamamelis virginiana* L. (Hamamelidaceae).

Folium Hamamelidis consists of the dried (*1*, *2*) or fresh leaves (*3*), and Cortex Hamamelidis consists of the dried bark of the trunk and twigs of *Hamamelis virginiana* L. (*2*, *4*).

## Synonyms

*Hamamelis androgyna* Walt., *H. caroliniana* Walt., *H. corylifolia* Moench., *H. dentata* Moench., *H. dioica* Walt., *H. estivalis* Raf., *H. macrophylla* Pursh., *H. nigra* Raf., *H. parvifolia* Raf., *H. rotundifolia* Raf., *H. virginata* sic, *H. virginiae* L., *H. virginiana* ssp. *parvifolia* Nutt., *H. virginica* L., *Trilopus dentata* Raf., *T. estivalis* Raf., *T. nigra* Raf., *T. parvifolia* Raf., *T. rotundifolia* Raf., *T. virginica* Raf. (*5*, *6*).

## Selected vernacular names

Amamelide, Amerikamansaku, cortice de hamamelis, feuilles d'hamamélis, feuilles du noisetier de la sorcière, folhas de hamamelis, hamamelis, hamamélis de virginie, Hexenhasel, magician's rod, noisetier de sorcière, oczar, pistachio nut, snapping hazelnut, spotted alders, striped alder, tobacco wood, varázsdió levél és kéreg, vilin virginsky, virginische Zaubernuss, virginischer Zauberstrauch, white hazel, winter bloom, witch hazel, Zauberhasel, Zaubernuss (*5*–*8*).

## Geographical distribution

Indigenous to the Atlantic coast of North America, found in damp woods ranging from Nova Scotia to Florida and as far west as Texas (*6*, *8*, *9*).

## Description

A tall shrub or small tree, up to 4.6 m high. Branches highly branched. Leaves alternate, stipulate, short-petioled, unequilaterally ovate or rhomboid-ovate, with oblique base and sinuate or sinuate-dentate margin. Flowers thread-like, golden-yellow; appear in axillary clusters as leaves fall in autumn and at about the same time as fruits ripen from blossoms of the previous year. Fruit a

2-beaked, 2-celled, woody capsule dehiscing loculicidally from the top, each cell containing a single black seed (*8*, *10*, *11*).

## Plant material of interest: dried and fresh leaves, dried bark

### *General appearance*

#### Folium

Green or greenish-brown, often broken, crumpled and compressed into more or less compact masses. Lamina 5–12 cm long, 3–8 cm wide, broadly ovate to obovate; base oblique and asymmetric; apex acute or, rarely, obtuse; margins of lamina roughly crenate or dentate. Venation pinnate and prominent on the abaxial surface; usually 4–6 pairs of secondary veins attached to main vein, leaving at an acute angle and curving gently to marginal points where there are fine veins often at right angles to secondary veins (*1*).

#### Cortex

Channelled, seldom quilled or in strips, up to 3 cm wide and 2 mm thick. Outer surface light yellowish-brown or reddish-brown, has thin, whitish or greyish-brown cork with numerous lenticels; inner surface yellowish-brown to reddish-brown, longitudinally striated. Fracture splintery and fibrous (*9*).

### *Organoleptic properties*

#### Folium

Odour: slight; taste: astringent, slightly aromatic, bitter (*8*).

#### Cortex

Odourless; taste: strongly astringent, slightly bitter (*2*, *9*).

### *Microscopic characteristics*

#### Folium

Upper epidermis of leaf composed of slightly elongated cells with straight to slightly sinuous walls; walls moderately and sometimes unevenly thickened; no stomata; underlying palisade cells fairly small and distinct. Lower epidermis composed of polygonal cells with very sinuous outline; walls thinner and more uniform than those of upper epidermis; paracytic stomata fairly numerous but rather faint and indistinct; underlying cells of spongy mesophyll frequently brown, appear as clearly defined honeycomb network. Covering trichomes characteristic, stellate, found fragmented, occasionally entire, composed of 4–12 elongated, conical cells united at their bases to form a radiating structure; each cell has moderately and slightly unevenly thickened wall which is slightly lignified. Linear idioblasts, composed of lignified cells, found scattered across

entire thickness of lamina. Prismatic calcium oxalate crystals scattered, occasionally found in clusters, as well as forming a sheath (*12*).

**Cortex**

Sclereids abundant, vary considerably in size, are of 2 types: rounded to oval, or subrectangular; heavily thickened, usually in groups of just 2 or 3 cells, but smaller cells often form larger groups; walls have numerous, conspicuous branched pits and striations, particularly in the larger cells; other type of sclereids more regular in size and form, frequently found associated with the cork, occurring as a layer of small, polygonal cells with no intercellular spaces. Fibres occur in groups surrounded by a sheath of prismatic calcium oxalate crystals; individual fibres very thick-walled and lignified with indistinct lumen with calcium oxalate prismatic crystals scattered as well as in the parenchyma surrounding the fibres. Crystals also occasionally found associated with thicker-walled sclereids; crystals fairly uniform in size, although a few very large prisms may occur. Parenchyma cells thin-walled, several filled with dark brown contents. Medullary rays uniseriate, composed of rounded cells with slightly thickened walls. Cork cells thin-walled and polygonal. Fragments of lignified xylem tissue from adherent wood infrequent and consist of narrow tracheids with conspicuous bordered pits, accompanied by thin-walled fibres and pitted medullary ray cells. Starch grains rare; a few small, spherical grains may be found in some parenchymatous cells (*12*).

### *Powdered plant material*

**Folium**

Brownish-green; fragments of adaxial epidermis with wavy anticlinal walls; abaxial epidermis with stomata, some paracytic, others atypical; covering trichomes, stellate, either entire or broken, composed of 4–12 cells united at their bases; cells elongated and conical, usually up to 250 μm long, thick-walled with clearly visible lumen with often brown contents. Fibres lignified and thick-walled, isolated or in groups; accompanied by sheath of prismatic calcium oxalate crystals. Parenchymatous palisade cells small and cylindrical; irregular-shaped cells of spongy mesophyll; sclereids, frequently enlarged at one or both ends, 150–180 μm long, whole or fragmented; fragments of annular or spiral vessels; isolated prismatic calcium oxalate crystals (*1*).

**Cortex**

Masses of brownish or yellowish cork cells, some lignified; groups of parenchyma cells with tannin or small starch grains; strands of lignified bast; tracheae with bordered pores; strongly lignified wood fibres with slit-like or bordered pores; crystal fibres containing monoclinic prismatic calcium oxalate crystals (up to 40 μm in length) (*13*).

## General identity tests

Macroscopic and microscopic examinations (*1*), thin-layer chromatography (*1*, *2*) and high-performance liquid chromatography (*5*) for characteristic tannin constituents.

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

### *Foreign organic matter*

**Folium**

Not more than 7% stems, and not more than 2% other foreign matter (*1*).

**Cortex**

Not more than 2% foreign matter (*2*, *4*).

### *Total ash*

**Folium**

Not more than 7% (*1*).

**Cortex**

Not more than 6% (*2*).

### *Acid-insoluble ash*

**Folium**

Not more than 2% (*1*).

**Cortex**

Not more than 1.5% (*2*).

### *Alcohol-soluble extractive*

**Folium**

To be established in accordance with national requirements.

**Cortex**

Not less than 20% using 45% alcohol (*2*).

### *Loss on drying*

**Folium**

Not more than 10% (*1*).

**Cortex**

Not more than 12% (*4*).

### *Pesticide residues*

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

### *Heavy metals*

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

### *Radioactive residues*

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

### *Other purity tests*

**Folium and Cortex**

Chemical, sulfated ash and water-soluble extractive tests to be established in accordance with national requirements.

**Folium**

Alcohol-soluble extractive test to be established in accordance with national requirements.

## Chemical assays

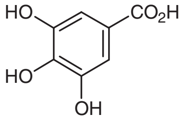
Folium: contains not less than 3% tannins (*1*). Cortex: contains not less than 4% tannins (*4*). Thin-layer chromatography is used for qualitative and quantitative analysis of tannins (*1*). A high-performance liquid chromatography method for quantitative analysis of condensed and hydrolysable tannins has been developed (*17*, *18*).

## Major chemical constituents

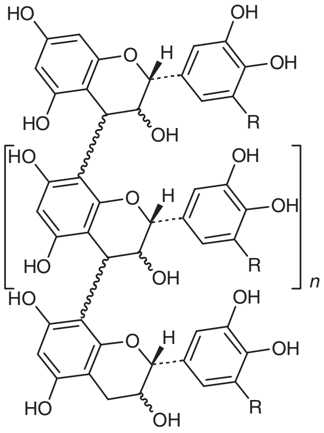
The major constituents of the dried leaf and bark are tannins (up to 10%). Both hydrolysable and condensed tannins are present, with the latter predominating (*9*, *11*, *19*). Folium tannins are a mixture of gallic acid (10%), hydrolysable

hamamelitannin (1.5%) and condensed proanthocyanidins (88.5%) (*17*). Cortex tannins are similar qualitatively, but have a much higher hamamelitannin level (up to 65% of a hydroalcoholic extract) (*11*).

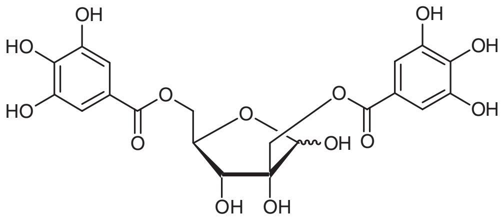
The structures of gallic acid, hamamelitannin and condensed proanthocyanidins are presented below.




gallic acid




proanthocyanidins
procyanidin $n = 0$, R = H
prodelphinidin $n = 0$, R = OH




hamamelitannin

## Medicinal uses

### *Uses supported by clinical data*

Topically for minor skin lesions, bruises and sprains (*3*, *5*, *20*), local inflammation of the skin and mucous membranes (*3*, *5*, *20–24*), haemorrhoids (*3*, *5*, *20*, *25–28*) and varicose veins (*3*).

### *Uses described in pharmacopoeias and in traditional systems of medicine*

Topically as a haemostat (*27*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of colitis, diarrhoea, dysentery, dysmenorrhoea, eye inflammations, haematuria, kidney pains, neuralgia, nosebleeds and excessive menstruation. Also as a tonic (*6*, *7*, *19*).

# Pharmacology

## *Experimental pharmacology*

### Astringent activity

The phenolic constituents of Folium et Cortex Hamamelidis, particularly the tannins (e.g. hamamelitannin), aldehydes and oligomeric proanthocyanidins, are responsible for its astringent activity (*6, 18, 29, 30*). Similar to other astringent drugs, application of Hamamelidis[1] preparations to the skin and mucosa in low concentrations sealed cell membranes and reduced capillary permeability (*6, 30*). Higher concentrations precipitated proteins and thickened colloidal tissue, forming a thin membrane in the wound region, and slightly compressed the skin tissue beneath it (*6*). Alcohol extracts of Hamamelidis had strong astringent action, with the bark extract being slightly superior to the leaf extract (*31*).

The healing effect of Hamamelidis distillate was compared with hydrogen peroxide on skin damaged by application of dichlorodiethyl sulfide (mustard gas) in various animal models. The distillate was more effective than hydrogen peroxide in reducing the occurrence of pus in the affected skin areas. Furthermore, subsequent treatment of the purulent skin areas with a 20% Hamamelidis ointment reduced the incidence of suppuration as compared with hydrogen peroxide treatment (*6, 32*).

### Venotonic activity

The venotonic effects of leaf preparations (steam distillate, tincture or alcohol extract) were tested by measuring the blood supply to the rear paw of rabbits (33). A decrease in blood supply was observed after intra-arterial administration of the distillate. This effect was not influenced by concomitant administration of adrenergic, adrenolytic or myotonic drugs (*33–35*).

### Antibacterial activity

An aqueous extract of the leaves inhibited the growth in vitro of *Escherichia coli* (MIC 0.4 mg/ml), *Staphylococcus aureus* (MIC 0.4 mg/ml), *Bacillus subtilis* (MIC 1.1 mg/ml) and *Enterococcus faecalis* (MIC 3.0 mg/ml). Aqueous extracts of the bark inhibited the growth in vitro of *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Enterococcus faecalis* (MIC for all 10.0 mg/ml) (*36*).

### Antioxidant activity

Hamamelitannin inhibited the production of superoxide anion radicals ($IC_{50}$ 1.38 µmol/l) and hydroxyl radicals ($IC_{50}$ 5.46 µmol/l), as measured by electron spin resonance spectrometry (*37, 38*). Hamamelitannin also suppressed the depolymerization of hyaluronic acid and protected human dermal fibroblasts against damage induced by superoxide anion radicals (at concentrations of

[1] Refers to Folium et Cortex Hamamelidis.

1 mmol/l and 10 mmol/l, respectively) (*37*). Hamamelitannin and gallic acid protected murine dermal fibroblasts against damage induced by superoxide anion radicals ($IC_{50}$ 1.31 µmol/l and 1.01 µmol/l, respectively) (*38*). Both tannins had free radical scavenging activity. For superoxide anion scavenging, the $IC_{50}$ was 1.31 µmol/l for hamamelitannin and 1.01 µmol/l for gallic acid, compared with 23.31 µmol/l for ascorbic acid. For hydroxyl radical scavenging, the $IC_{50}$ was 5.46 µmol/l for hamamelitannin and 78.04 µmol/l for gallic acid. For singlet oxygen scavenging, the $IC_{50}$ was 45.51 µmol/l for hamamelitannin and 69.81 µmol/l for gallic acid (*39*).

### *Anti-inflammatory activity*

Hamamelidis extracts and isolated chemical constituents have anti-inflammatory activity both in vitro and in vivo. Intraperitoneal administration of a 70% ethanol extract of the leaves (200 mg/kg body weight) significantly inhibited the chronic phase of carrageenan-induced rat footpad oedema (*40*). Hamamelitannin and galloylated proanthocyanidins isolated from Hamamelidis are potent inhibitors of 5-lipoxygenase ($IC_{50}$ range 1.0–18.7 µg/ml). Topical application of a hydroalcoholic extract of the bark (250 µg/ml) inhibited croton oil-induced ear oedema in mice. In addition to anti-inflammatory activity, this study demonstrated that the proanthocyanidin fraction of the hydroalcoholic extract was active against herpes simplex virus type 1 ($ED_{50}$ 11 µg/ml), and also inhibited α-glucosidase ($ED_{50}$ 0.35 µg/ml) and human leukocyte elastase ($ED_{50}$ 1.4 µg/ml) (*41*).

## *Clinical pharmacology*

### Anorectal complaints

The astringent properties of Hamamelidis extracts have led to their use in ointments and suppositories for the treatment of anorectal complaints, such as haemorrhoids (*25–27*). In a clinical study without controls of 75 patients with acute stage 1 haemorrhoidal symptoms, the efficacy of rectal ointments containing either a Hamamelidis fluidextract or bismuth subgallate was assessed. After application of either ointment twice daily for 3 days, significant improvement was observed in pruritus, burning sensation and pain ($P < 0.001$). Marked recovery was noted after 3 weeks of therapy (*25*). A randomized, double-blind trial compared the efficacy of rectal ointments containing either a Hamamelidis fluidextract, bismuth subgallate or a local anaesthetic in the treatment of 90 patients with acute stage 1 haemorrhoidal symptoms. The local anaesthetic was present in two control ointments which also contained either policresulen or fluocinolone acetonide. After 21 days of treatment, all four ointments were equally effective in improving pruritus, bleeding, burning sensation and pain (*26*).

The efficacy of a Hamamelidis ointment containing 25 g aqueous distillate/100 g ointment base (equivalent to about 4 g drug) was compared to a Hamamelidis reference preparation in a study without controls of 70 patients

with various anorectal complaints. Preparations were applied to the affected skin or transitional mucosa three times daily either alone or in combination with sclerotherapy. After 4 weeks of treatment, symptoms such as pruritus, burning sensation and pain were eliminated in 60% of the patients treated with the Hamamelidis ointment (*28*).

**Anti-inflammatory activity**

The anti-inflammatory efficacy of an aftersun lotion containing 10% Aqua Hamamelidis was compared with that of two Hamamelidis-free aftersun lotions in 30 healthy volunteers. Each volunteer received four doses of ultraviolet B in a modified ultraviolet B erythema test. Chromametry and visual scoring were used to determine the degree of erythema at 7, 24 and 48 hours after irradiation. The lotion containing Hamamelidis suppressed erythema by 20% at 7 hours and by 27% at 48 hours, whereas the degree of suppression seen with the Hamamelidis-free lotions was 11% and 15%, respectively (*42*).

A randomized, double-blind study of 48 patients assessed the anti-inflammatory efficacy of topical application of a Hamamelidis distillate in a phospholipid-containing vehicle, hydrocortisone, camomile and four drug-free vehicle-based preparations. Erythema induced by ultraviolet light or repeated stripping of the skin with adhesive tape was suppressed only by the Hamamelidis preparation (0.64 mg or 2.5 mg Hamamelidis ketone per 100 g vehicle) and hydrocortisone cream (1%). However, the hydrocortisone cream was superior to all other preparations tested (*21*).

***Vasoconstriction***

A randomized, placebo-controlled study assessed the vasoconstrictive effects of an aqueous propylene glycol extract of Hamamelidis in 30 healthy volunteers. The extract produced a reduction in skin temperature as compared with the placebo (*6*, *43*). The anti-inflammatory effects of a Hamamelidis ointment containing 25 g aqueous distillate/100 g ointment base (about 4 g drug) were analysed in five patients with dermatoses and 22 healthy volunteers. Fluvography measurements indicated that in both groups the ointment reduced the thermal conductivity of the skin due to vasoconstriction, suggesting a mild anti-inflammatory activity. These data were confirmed by transcutaneous oxygen measurements (*44*).

***Eczema***

A randomized, double-blind, placebo-controlled trial compared the efficacy of three creams containing either a Hamamelidis distillate, 0.5% hydrocortisone or a drug-free vehicle in the symptomatic treatment of 72 patients with moderately severe atopic eczema. All treatments reduced the incidence of itching, scaling and erythema after 1 week of treatment: the cream containing Hamamelidis distillate was no more effective than that containing the placebo (*45*).

The efficacy of two Hamamelidis ointments (differing only in the ointment base), containing 25 g aqueous distillate/100 g ointment base (equivalent to about 4 g drug), for the treatment of endogenous eczema (neurodermatitis) and toxic degenerative eczema (attrition eczema) was compared in a placebo-controlled, double-blind study (the placebo was not described). Symptomatic improvements in itching, redness, burning sensation and desquamation of the skin were observed in the 36 patients with endogenous eczema (neurodermatitis) with both Hamamelidis preparations after treatment for 39 days. Eighty patients with toxic degenerative eczema (attrition eczema) treated with the Hamamelidis ointments showed improvements in rough skin, redness, burning sensation and desquamation of the skin after 28 days of treatment (*23*).

A randomized, double-blind comparison study assessed the efficacy of ointments containing either a standardized extract of the dried leaves or bufexamac in the treatment of 22 patients with bilateral, moderately severe endogenous eczema (neurodermatitis). Patients were treated three times daily for an average of 17 days. Comparison of the patients' forearms showed that both treatments reduced the severity of symptoms such as desquamation of the skin, redness, itching and lichenification, with desquamation showing the highest reduction (55%). No differences were observed in the global assessment of the therapy or the severity of symptoms between treatments (*24*).

In a pilot study of 37 patients with endogenous eczema (neurodermatitis), a cream containing a Hamamelidis leaf extract was applied twice daily for 2 weeks. Following treatment, considerable improvement in symptoms such as inflammation and itching was noted in 24 patients (*46*).

### *Analgesic activity*

In a randomized clinical trial involving 266 patients undergoing episiotomy, the efficacy of three analgesic treatments was investigated to determine their effects on pain, bruising and oedematous swelling. The treatments tested were local application of: a cream containing Hamamelidis water BPC 1973; a reference cream containing 1% hydrocortisone and a local anaesthetic; and ice packs. Oral paracetamol and salt baths were also used as needed. The efficacy of all three analgesic treatments appeared to be equal (*22*).

## Antiviral activity

The efficacy and safety of an ointment prepared with a special extract from the bark was assessed in a randomized, double-blind, placebo-controlled study for the treatment of herpes labialis infection. Thirty-four patients were treated within 48 hours of recurrence of symptoms, and treatment (daily) lasted for 8 days. By the end of the therapy, the size of the inflamed area was significantly reduced in patients treated with the Cortex Hamamelidis ointment as compared with placebo treatment ($P = 0.022$) (*47*).

## Contraindications

No information available.

## Warnings

No information available.

## Precautions

### *Carcinogenesis, mutagenesis, impairment of fertility*

Aqueous extracts of the dried leaves were not carcinogenic when administered subcutaneously to rodents (10 mg/animal) (*48*).

### *Other precautions*

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Folium et Cortex Hamamelidis should not be administered during pregnancy or lactation or to children without medical supervision.

## Adverse reactions

Allergic contact dermatitis may occur in sensitive individuals (*49*, *50*).

## Dosage forms

Dried leaves and bark for decoctions; steam distillate, ointment and suppositories (*3*, *9*). Fresh leaves and twigs are collected in the spring and early summer to make a steam distillate (*3*). Store in a well-closed container, protected from light (*19*).

## Posology

(Unless otherwise indicated)
External use: steam distillate, undiluted or diluted 1 : 3 with water to make poultices; 20–30% in semisolid preparations (*3*). Extracts: in semisolid and liquid preparations corresponding to 5–10% of the crude drug (*3*, *5*). Crude drug: decoctions from 5–10 g to 1 cup (250 ml) water for poultices and wound irrigation (*3*, *5*). Rectal suppositories: 1–3 times daily the quantity of a preparation corresponding to 0.1–1.0 g crude drug, use Hamamelidis water undiluted or diluted 1 : 3 with water (*3*, *5*). Other preparations: several times daily, corresponding to 0.1–1.0 g drug in preparations, or witch hazel water undiluted or diluted with water (*3*).

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# Semen Hippocastani

## Definition

Semen Hippocastani consists of the dried ripe seeds of *Aesculus hippocastanum* L. (Hippocastanaceae) (*1, 2*).

## Synonyms

*Aesculus castanea* Gilib., *A. procera* Salisb., *Castanea equina*, *Hippocastanum vulgare* Gaertner (*3*). Not to be confused with the common chestnut, *Castanea dentata* (Marshall) Burkh. (Fagaceae) (*4*) or related *Castanea* species (*5*).

## Selected vernacular names

Abu farwat el hhussan, castagna amare, castagna cavallina, castagna di cavalle, castagno d'India, castan, castandas da India, castanheiro da India, castaño de Indias, chata, châtaignier de cheval, châtaignier de mer, common horse chestnut, conqueror tree, custul, gemeine Kastanie, gemeine Rosskastanie, hippocastani semen, horse chestnut, karu, marronier d'Inde, naru, paardekastanje, Pferdekastanie, qastanah baria, Rosskastanie, seiyo-tochinoki, seiyoutochinoki, semen castaneae equinae, shahbalout-e hendi, vadgesztenyemag, weisse Rosskastanie, wilde kastanje, wilde kest (*3, 6*).

## Geographical distribution

Indigenous to western Asia, is now widely cultivated in parks, gardens and along city streets of many countries worldwide, including those in Europe, and the United States of America (*7*).

## Description

A tree, up to 30 m high and 2 m in circumference, with large sticky buds and dense, broad, usually orbicular, or occasionally pyramidal, crown. Leaves up to 20 cm long and 10 cm wide, with 15–20 cm long petioles; composed of 5–7 large sessile leaflets, median leaflet largest, outer leaflets much smaller. Blades obovate or oblong, tapering at the base, abruptly mucronate, irregularly serrate at the margin; dorsal side glabrous; ventral side with soft hairs. Flowers have 5 petals with an orbicular limb, imbricate at the margins, white, with yellow spot at base which later turns pink; arranged in erect dense panicles up to 20–

30 cm long; rachis and pedicel with reddish-brown hairs; calyx cylindrical to campanulate and pubescent; stamens hairy at the base; ovary covered with soft hairs and prickles. Capsules spiny, usually with 1 large seed (*7*).

## Plant material of interest: dried ripe seeds

### *General appearance*

Globulous or ovoid, 2–4 cm in diameter. The 2 large cotyledons fleshy, oily and starchy, often connate with a line of suture more or less visible; covered by a shiny dark-brown tegument with a large whitish spot corresponding to the hilum; tegument creamy white in the immature seed, takes on a brown tinge during maturation, becoming dark brown when mature. Curved radicle occupies a depression either on the commissure of the cotyledons or on the dorsal side of 1 of the cotyledons (*1*, *2*).

### *Organoleptic properties*

Odour: slight; taste: bitter, acrid (*1*).

### *Microscopic characteristics*

Seed envelope made up of polygonal cells radially oriented in a transverse section of the seed. Underneath the envelope are numerous layers of sclerenchyma cells with dense, roughly mottled, yellowish-brown thick walls; loose parenchyma, colourless, consisting of a few layers of cells, with rigid walls; sparse annulate or spiral vessels. Tissue of the cotyledons made up of cells with thin, colourless walls, full of starch and lipids. Characteristic starch grains found singly, either spherical (15–25 µm in diameter) or irregular (pear- or kidney-shaped); also numerous small (5–10 µm in diameter), spherical starch grains and a few grains clustered into groups of 2–4 (*1*, *2*).

### *Powdered plant material*

Yellowish-grey. Characteristic starch grains found singly, either spherical (15–25 µm in diameter) or irregular (pear- or kidney-shaped); also numerous small (5–10 µm in diameter), spherical starch grains and a few grains clustered into groups of 2–4. Oil droplets of different sizes; fine fragments of colourless cell walls from the cotyledons; fragments of seed envelope brownish-yellow; and parenchyma and roughly mottled sclerenchyma cells (*1*).

## General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for the characteristic triterpene saponin, aescin (also known as escin) (*1*, *2*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO quality control methods for medicinal plants (*8*).

### *Foreign organic matter*

Not more than 2% (*1*).

### *Total ash*

Not more than 4% (*1*, *2*).

### *Loss on drying*

Not more than 10% (*2*).

### *Pesticide residues*

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*9*). For other pesticides, see the *European pharmacopoeia* (*9*), and the WHO guidelines on quality control methods for medicinal plants (*8*) and pesticide residues (*10*).

### *Heavy metals*

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*8*).

### *Radioactive residues*

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*8*) for the analysis of radioactive isotopes.

### *Other purity tests*

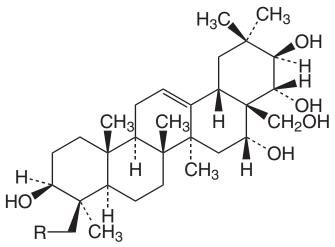
Chemical, acid-insoluble ash, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

## Chemical assays

Contains not less than 3.0% triterpene saponins, calculated as aescin (escin), determined by spectrophotometry at 540 nm (*1*, *2*). High-performance liquid chromatography (*11*) and thin-layer chromatography–densitometry (*11*, *12*) procedures for the quantitative analysis of triterpene saponins have also been developed.

## Major chemical constituents

The major constituents are triterpene saponins (up to 10%), collectively referred to as aescin (also known as escin), and are considered the active therapeutic principles. Aescin exists in three forms, α-aescin, β-aescin and cryptoaescin, which are differentiated by their physical properties. β-aescin is a mixture of more than 30 different glycosides derived from the triterpene aglycones protoaescigenin (also known as protoescigenin) and barringtogenol C. Other constituents include flavonoids (e.g. quercetin, kaempferol and their glycosyl derivatives) (*3, 5, 7*). The structures of barringtogenol C and protoaescigenin are presented below.




barringtogenol C R = H
protoaescigenin R = OH

## Medicinal uses

### *Uses supported by clinical data*

Internally, for treatment of symptoms of chronic venous insufficiency, including pain, feeling of heaviness in the legs, nocturnal calf-muscle spasms, itching and oedema (*13–21*). Externally, for the symptomatic treatment of chronic venous insufficiency, sprains and bruises (*22–24*).

### *Uses described in pharmacopoeias and in traditional systems of medicine*

Treatment of coronary heart disease (*25*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of bacillary dysentery and fevers. Also as a haemostat for excessive menstrual or other gynaecological bleeding, and as a tonic (*6*).

## Pharmacology

### *Experimental pharmacology*

#### Anti-inflammatory activity

Intravenous administration of a 95% ethanol extract of Semen Hippocastani (0.2–0.4 ml/kg body weight) decreased histamine-induced erythema in guinea-pigs (*26*). Intragastric administration of a 30% ethanol extract of the seeds sup-

pressed carrageenan-induced footpad oedema and adjuvant-induced arthritis in rats (at doses of 0.6 and 1.5 ml/kg body weight, respectively) (*27*). Intraperitoneal administration of a saponin fraction isolated from a seed extract exhibited analgesic, anti-inflammatory and antipyretic activities in vivo; the saponin fraction also inhibited prostaglandin synthetase activity in vitro (*28*). Intragastric administration of a hydroalcoholic extract of the seeds to rats (200–400 mg/kg body weight) suppressed footpad oedema induced by peroxide and carrageenan (*29*). Intravenous or oral administration of aescin to rats (0.5–120 mg/kg body weight) inhibited footpad oedema induced by dextran, and granuloma induced by cotton pellet and formalin paper (*30–32*). Intravenous administration of aescin to rats reduced footpad oedema induced by ovalbumin, formalin and dextran (*33*, *34*).

### Vasoactive effects

A hydroalcoholic extract of the seeds induced contractions in canine saphenous veins in vitro, and an intravenous bolus (25–50 mg) increased venous pressure in perfused canine saphenous veins in vivo (*29*).

Cutaneous capillary hyperpermeability induced by chloroform, serotonin and histamine also decreased in rats and rabbits after intragastric administration of a hydroalcoholic extract of the seeds (50–400 mg/kg body weight) (*29*). Aescin (5–10 μg/ml) increased the tension of isolated human saphenous veins and rabbit portal veins in vitro. The effect was due to preferential formation of prostaglandin $F_{2\alpha}$ and was reversed by treatment with indometacin (*35*). The vasoactive effects of aescin were investigated in isolated peripheral blood vessels, isolated arteries and veins (constant-flow perfused cat rear paw, isolated perfused carotid artery of the guinea-pig and iliac veins of the pig). Aescin had a biphasic effect on blood vessels: initial transient dilation was followed by increased tone, which was long lasting in isolated arteries and veins, but was transient in isolated peripheral blood vessels (*36*). Aescin has also been shown to inhibit hyaluronidase activity in vitro ($IC_{50}$ 149.9 μmol/l) (*37*). A hydroalcoholic extract of the seeds (250 μg/ml) reduced lipid peroxidation and had radical-scavenging properties ($IC_{50}$ 0.24 μg/ml for superoxide dismutase radicals) (*38*).

## *Clinical pharmacology*

### Chronic venous insufficiency and related conditions

Nine placebo-controlled clinical trials (eight double-blind, one single-blind, seven with crossover design) assessed the efficacy of oral administration of a standardized Semen Hippocastani extract (250–600 mg, equivalent to 100–150 mg aescin daily) in a sustained-release form for the symptomatic treatment of patients with chronic venous insufficiency (CVI) (*13–21*). In one study, 96 patients with CVI received the extract over two treatment periods of 20 days each. Symptomatic improvement in skin colour, venous prominence, oedema, dermatosis, and pain, itching and feeling of heaviness in the legs were observed

in the treated patients (*13*). However, the methodology of this study was poor, and no statistical analysis was performed. Two later studies assessed the efficacy of the extract in 212 patients (*19*) and 95 patients (*17*) with CVI, using a numerical scale to rate the severity of symptoms. A significant symptomatic improvement ($P < 0.01–0.05$) in oedema, calf-muscle spasms, pain and feeling of heaviness in the legs was observed in patients treated with the extract (during two treatment periods of 20 days each) (*17, 19*). The efficacy of the extract was assessed in a double-blind study of 20 female patients (13 with pregnancy-related varicose veins and seven with CVI) during two treatment periods of 14 days each. A significant reduction in leg volume (114 ml in patients with varicose veins and 126 ml in patients with CVI, $P < 0.01$) was demonstrated by water plethysmography in patients treated with the extract (*21*). Another double-blind study assessed the efficacy of the extract in the treatment of 74 patients with CVI and lower-leg oedema. In patients treated with the extract, the leg volume following induction of oedema was reduced from 32 ml to 27 ml (determined by water plethysmography); in the placebo group the leg volume increased from 27 ml to 31 ml (*18*).

Two further studies investigated the effects of the extract on the intravascular volume of the lower-extremity veins and on interstitial filtration (measured indirectly by venous-occlusion or water plethysmography) in patients with CVI (*14, 20*). In one of the studies, after a single dose of 600 mg extract (equivalent to 100 mg aescin), the transcapillary filtration coefficient decreased by 22%, as compared with a slight increase in the coefficient of the placebo group. This study demonstrated that the extract exerted its action primarily by reducing capillary permeability (*14*). In the other study, patients treated daily with 600 mg extract (equivalent to 100 mg aescin) for 28 days showed a significant reduction in extravascular volume of the foot and ankle ($P < 0.01$), as well as a significant improvement in oedema, and feelings of tension, pain, fatigue and itching of the legs ($P < 0.05$). However, no changes in venous capacity or calf-muscle spasms were observed (*20*).

The efficacy of the extract was assessed in a randomized, parallel, double-blind study of 40 patients with venous oedema due to chronic deep-vein incompetence stage II. Patients received 369–412 mg extract (equivalent to 75 mg aescin) twice daily for 6 weeks. A significant reduction was observed in leg volume (measured by water plethysmography after oedema induction) and leg circumference in the treated group ($P < 0.01$) (*15*). A randomized, single-blind, parallel study compared the efficacy and safety of class II compression stockings with the extract or placebo in 240 patients with CVI. Patients in the treatment group received 300 mg extract (equivalent to 50 mg aescin) twice daily for 12 weeks. The lower-leg volume of the affected limbs decreased by an average of 43.8 ml in patients treated with the extract and by 46.7 ml in patients wearing compression stockings. In the placebo group, the lower-leg volume increased by 9.8 ml. Thus, treatment with the extract or wearing class II compression stockings resulted in similar decreases in lower-leg volume (*16*).

A randomized, double-blind trial compared the efficacy of a standardized extract (360–412 mg, equivalent to 75 mg aescin, twice daily) and oxerutins (1000 mg *O*-(β-hydroxyethyl)-rutinosides twice daily) in 40 patients with CVI and peripheral venous oedema. A reduction in oedema (based on measurement of leg circumference) was observed in both treatment groups (*39*). Another randomized, double-blind study compared the efficacy of a standardized seed extract with oxerutins in the treatment of 137 postmenopausal women with chronic deep-vein incompetence stage II. Following a 1-week placebo run-in, patients were treated daily with either 600 mg extract (equivalent to 100 mg aescin) or 1000 mg oxerutins for 12 weeks, or 100 mg oxerutins for 4 weeks followed by 500 mg oxerutins for 12 weeks. Patients were observed for 6 weeks after treatment; the group treated with 1000 mg oxerutins had the greatest decrease in leg volume (*40*).

A placebo-controlled, double-blind crossover study assessed the effect of a standardized seed extract in the symptomatic treatment of 52 pregnant women with venous insufficiency. Patients were treated with either one capsule containing 300 mg extract (equivalent to 50 mg aescin) or a placebo twice daily for 2 weeks. The extract was superior to the placebo in reducing oedema and symptoms such as leg pain, fatigue and itching. Patients treated with the extract also showed a greater resistance to oedema induction (*41*). The ability of a standardized seed extract to reduce oedema was investigated in a randomized, double-blind, placebo-controlled trial of 30 patients with CVI. A significant reduction in leg circumference was found in the treatment group ($P < 0.05$) as compared to the placebo group ($P < 0.05$) (*42*).

A double-blind placebo-controlled study investigated the effect of a standardized seed extract (one dose of 600 mg, equivalent to 100 mg aescin) on vascular capacity and filtration in the arms and legs of 12 healthy volunteers. Using vein plethysmography, the study showed a decrease in both vascular capacity and filtration coefficient in subjects treated with the extract (*43*). The effect of a standardized seed extract (one dose of 1800 mg) on the flow velocity of venous blood between the instep and the groin was quantitatively determined in 30 patients with varicose veins by the xenon-133 appearance method. Blood flow increased by >30%, with a lasting effect observed after 12 days of treatment. Blood viscosity was also reduced and there was a 73% improvement in subjective complaints (*44*). A randomized double-blind study assessed the effect of a standardized seed extract on lower-leg oedema in 10 healthy volunteers during a 15-hour airflight. A single dose of the extract (600 mg, equivalent to 100 mg aescin) completely prevented or significantly reduced the increase in ankle and foot oedema ($P < 0.05$), determined by measuring the circumference of the ankle and heel before and after flying (*45*). A postmarketing surveillance study of over 5000 patients suffering from CVI demonstrated that treatment with a standardized seed extract (equivalent to 75 mg aescin) twice daily for 4–10 weeks reduced the symptoms of leg pain, fatigue, oedema and itching (*46*). In a multicentre study without controls, 71 patients with CVI were treated daily with a topical gel containing 2% aescin. After

6 weeks of treatment, a significant reduction in ankle oedema (reduction of 0.7 cm in the ankle circumference, $P < 0.001$) and a significant reduction in the symptom score (60%, $P < 0.001$) was reported (*24*). In a postmarketing surveillance study involving over 4000 patients with CVI, treatment with a standardized extract of the crude drug (equivalent to 50 mg aescin) twice daily improved typical symptoms in more than 85% of patients (*47*).

A criteria-based systematic review assessed the randomized, double-blind, placebo-controlled trials of standardized seed extracts for symptomatic treatment of CVI. The data were extracted from the trials in a standardized manner, and the methodological quality and outcome of each trial were assessed by two independent reviewers. In all trials, the extract was shown to be superior to the placebo. Use of the extract was associated with a decrease in lower-leg oedema, and a reduction in the circumference of the calf and ankle. Other symptoms such as leg pain, itching and fatigue were reduced. Results from five comparative trials demonstrated that the extract was as effective as oxerutins, and one of the five trials showed that the extract was as effective as compression therapy (*48*).

**Bruises**

The efficacy of a topically applied gel containing 2% aescin in reducing the tenderness to pressure haematoma (experimentally induced by injection) was tested in a randomized, placebo-controlled, single-dose study involving 70 healthy volunteers. Based on tonometric sensitivity measurements, the aescin gel significantly reduced the tenderness to pressure haematoma ($P < 0.001$). This effect was seen 1 hour after treatment and lasted for 9 hours (*49*).

Other trials have assessed the efficacy and safety of a topically applied gel containing 2% aescin for the treatment of bruises and sprains (*22*, *23*).

## Contraindications

Semen Hippocastani is contraindicated in cases of known allergy to plants of the Hippocastanaceae family.

## Warnings

No information available.

## Precautions

### *Drug interactions*

Two suspected cases of toxic nephropathy probably due to very high doses of aescin were reported (*50*). Therefore, Semen Hippocastani should not be administered with other drugs known to be nephrotoxic, such as gentamicin.

### *Carcinogenesis, mutagenesis, impairment of fertility*

A 30% ethanol extract of Semen Hippocastani was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100

(200 µl/ml) (*51*). Sodium aescinate had no effect on the fertility of male rats (*52*).

### *Pregnancy: teratogenic effects*

A 40% ethanol extract of Semen Hippocastani was not teratogenic or embryotoxic in rats or rabbits following intragastric administration of 1.6 ml/kg body weight (*53*). Intragastric administration of a 40% ethanol extract of the seeds to rats (100–300 mg/kg body weight) or rabbits (100 mg/kg body weight) was not teratogenic. However, when pregnant rabbits were given 300 mg/kg body weight, a reduction in birth weight was observed (*54*).

### *Pregnancy: non-teratogenic effects*

Semen Hippocastani has been used in clinical trials involving pregnant women with no ill effects (*21*, *41*). However, the drug should not be administered during pregnancy without medical supervision.

### *Paediatric use*

There is no therapeutic rationale for the use of Semen Hippocastani in children.

### *Other precautions*

No information available on general precautions or precautions concerning drug and laboratory test interactions; or nursing mothers. Therefore, Semen Hippocastani should not be administered during lactation without medical supervision.

## Adverse reactions

Case reports have indicated gastrointestinal side-effects such as nausea and stomach discomfort (*47*, *55*). Allergic reactions have also been reported (*56*).

## Dosage forms

Crude drug and extracts (*7*). Store away from light and humidity (*1*).

## Posology

(Unless otherwise indicated)
Daily dosage: 250.0–312.5 mg twice daily of a standardized powdered extract of the crude drug (equivalent to 100 mg aescin) containing 16–20% triterpene glycosides, calculated as aescin (*55*); topical gels containing 2% aescin (*22–24*, *49*).

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# Herba Hyperici

## Definition

Herba Hyperici consists of the dried flowering tops or aerial parts of *Hypericum perforatum* L. (Clusiaceae) (*1–3*).

## Synonyms

*Hypericum officinarum* Crantz, *Hypericum officinale* Gater ex. Steud., *Hypericum vulgare* Lam. (*4*). Clusiaceae is also referred to as Guttiferae or Hypericaceae.

## Selected vernacular names

Balsana, bassan, bossant, common St John's Wort, corazoncillo, dendlu, devil's scourge, echtes Johanniskraut, Eisenblut, erba di San Giovanni, flor de sao joao, fuga daemonum, hardhay, Hartheu, herbe à mille trous, herbe de millepertuis, Herrgottsblut, Hexenkraut, hierba de San Juan, hiperico, hipericon, houfarighoun, iperico, Jageteufel, Johannisblut, Johanniskraut, John's wort, Jottannesort, klamath weed, Konradskraut, Liebeskraut, Lord God's wonder plant, Mannskraft, millepertuis, pelicao, perforata, perforate St John's wort, pinillo de oro, quian-ceng lou, St Jan's kraut, St John's Wort, seiyouotogiri, sint janskruid, tenturotou, Teufelsflucht, Tüpfelhartheu, witches's herb, zwieroboij (*2*, *4–7*).

### *Geographical distribution*

Indigenous to northern Africa, South Africa, South America, Asia, Australia, Europe and New Zealand, and is naturalized in the United States of America (*2*, *7*, *8*). The plant material is harvested at flowering time (*1*).

## Description

A herbaceous, aromatic perennial plant, up to 1 m high; glabrous throughout, green or sometimes glaucous. Stems rounded, 2-winged, erect and branched at top. Leaves oval, linear-oblong, broadly elliptic, subcordate, flat or more or less revolute-marginated with pellucid glands and sometimes a number of brown-black glandular dots. Flowers numerous, forming a broadly paniculate, compound cymose inflorescence. Petals oblong to oblong-elliptic, inequilateral with numerous glandular dots. Seed 1 mm long, cylindrical, brown, minutely pitted longitudinally (*2*, *8*, *9*).

## Plant material of interest: dried flowering tops or aerial parts

### *General appearance*

Stem glabrous greenish-yellow to brownish-yellow branching, 2-winged, cylindrical with 2 equidistant longitudinal bands. Leaves glabrous, generally sessile, opposite, greenish-grey, oval, 8–35 mm long, with entire margins; laminal margin often more or less revolute-marginated. Brown-black glandular dots sometimes present along the edges; numerous pellucid glands on the entire surface. Flowers, 2 cm in diameter, regular, forming a broadly paniculate, compound cymose inflorescence at top of stem, composed of: 5 green, lanceolate sepals, containing punctiform, black glandular dots on the edges; 5 golden-yellow petals, with numerous glandular dots along margins; and 3 staminal blades, each divided into multiple golden-yellow stamens. Anthers with single, terminal, dark pigment dot. Ovary elongated and conical, parietal placentation, carries 3 styles. Fruits trilocular capsules containing numerous brown, triangular seeds (*1–3*, *9*).

### *Organoleptic properties*

Odour: weak, aromatic, balsamic; taste: bitter, acrid (*9–11*).

### *Microscopic characteristics*

Transverse section of the stem circular and presents 2 lateral edges corresponding to the 2 longitudinal bands. From the exterior inwards are seen: epidermal layer formed of large polygonal cells; continuous collenchymal layer, slightly more developed at the 2 lateral edges; a cortical parenchyma containing crystals of calcium oxalate in the shape of a sea urchin; a ring of continuous phloem, distinct from the xylem, which consists of large vessels and a lignified parenchyma with a visible cambium; and a lacunose medullary parenchyma. Secretory pockets, almost invisible, rarely present in the endoderm. Upper surface of leaf section shows polygonal cells with sinuous, slightly beaded, anticlinal walls; cells of lower surface smaller, anticlinal walls more wavy with frequent paracytic, sometimes anomocytic, stomata; smooth cuticle, thicker on upper surface; straight-walled, elongated epidermal cells of veins occasionally beaded. Dorsoventral surface of leaf consists of a single palisade layer and large oil glands. Midrib shows single, collateral bundle with small area of lignified xylem. Microscopic characteristics of the sepal resemble those of the leaf. Petal narrow, elongated, thin-walled, epidermal cells with straight anticlinal walls on outer surface and wavy on inner surface. Stamen lignified fibrous layer of anther wall; elongated, thin-walled cells of filament with striated cuticle. Pollen grains spherical or elliptical, 20–28 µm in diameter, with 3 germinal pores and smooth exine. Ovary small polygonal cells

with underlying oil glands. Seed testa brown, thick-walled hexagonal cells (*2, 3, 9*).

### *Powdered plant material*

Yellowish-green or brownish-green. Leaf fragments abundant, most containing large characteristic hypericin oil glands with brown to red contents. Fragments of leaf epidermis, the adaxial side with thick-walled punctate, slightly sinuate cells, and abaxial side with sinuate cells and paracytic stomata; mesophyll fragments with large secretory pockets which are spherical, bright, containing strongly refractive oil droplets; fragments of palisade parenchyma; stem fragments with reticulate spiral vessels, areolate punctation, long fibres with thick walls, ligneous parenchyma, and small number of thick-walled, characteristically punctate medullary cells; fragments of petals made of elongated rectangular cells with irregular nodulous thickenings, containing numerous yellow droplets and large, round to oval secretory pockets; fragments of anthers; pollen grains 20–28 μm in diameter, smooth spherical or elliptical with 3 germinal pores; clusters of calcium oxalate crystals (*1, 2*).

## General identity tests

Macroscopic and microscopic examinations and thin-layer chromatography for the presence of characteristic compounds (hypericin, pseudohypericin, chlorogenic acid, hyperoside) (*1, 9–11*). Additionally, a liquid chromatography–mass spectrometry method is available (*12*). The presence of hyperforin and rutin in Herba Hyperici is used to differentiate *Hypericum perforatum* from other *Hypericum* species (*2*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

### *Foreign organic matter*

Not more than 3% stems with a diameter greater than 5 mm (*1*) and not more than 2% other foreign matter (*1, 3*).

### *Total ash*

Not more than 7% (*1*).

### *Acid-insoluble ash*

Not more than 2.5% (*9*).

### Sulfated ash
Not more than 2.5% (*9*).

### Water-soluble extractive
Not less than 12% (*9*).

### Loss on drying
Not more than 10% (*1*, *3*).

### Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

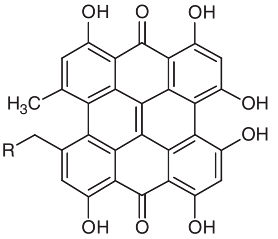
### Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

### Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

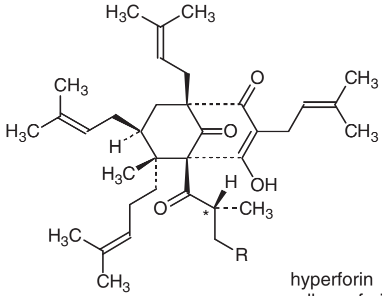
### Other purity tests
Chemical and alcohol-soluble extractive tests to be established in accordance with national requirements.

## Chemical assays
Contains not less than 0.08% hypericins calculated as hypericin, as determined by spectrophotometry (*1*). Quantitation can also be obtained by high-performance liquid chromatography (*2*, *16*).

## Major chemical constituents
The major characteristic constituents include 0.05–0.30% naphthodianthrones (hypericin, pseudohypericin, hyperforin, adhyperforin); 2–4% flavonoids (hyperoside, quercitrin, isoquercitrin, rutin); and 7–15% catechin tannins (*2*, *4*, *7*, *17*). The structures of the representative constituents are presented below.

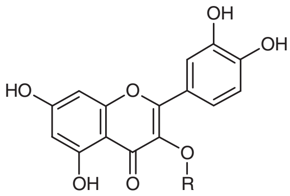



hypericin R = H
pseudohypericin R = OH



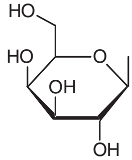

and epimer at C*

hyperforin R = H
adhyperforin R = $CH_3$



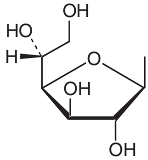

quercitrin R = Rha*p*
hyperoside R = Gal*p*
isoquercitrin R = Glc*f*
rutin R =Rha*p*-(1→6)-Glc*p*

Gal*p* =



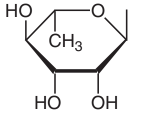

β-D-galactopyranosyl

Glc*f* =



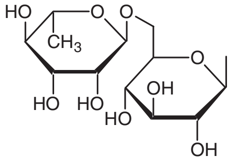

β-D-glucofuranosyl

Rha*p* =




6-deoxy-α-L-mannopyranosyl

Rha*p*-(1→6)-Glc*p* =




*O*-6-deoxy-α-L-mannopyranosyl-(1→6)-β-D-glucopyranosyl

# Medicinal uses

## *Uses supported by clinical data*

Symptomatic treatment of mild and moderate depressive episodes (classified as F32.0 and F32.1, respectively, in the *International statistical classification of diseases and related health problems, Tenth revision (ICD-10) (18)*) (*19–31*).

## *Uses reported in pharmacopoeias and in traditional systems of medicine*

Externally for the treatment of minor cuts, burns and skin ulcers (*8, 32*). Topically for viral infections (33).

### *Uses described in folk medicine, not supported by experimental or clinical data*

As an antiphlogistic agent in the treatment of inflammation of the bronchi and urogenital tract; treatment of biliary disorders, bladder irritation, the common cold, diabetes mellitus, dyspepsia, haemorrhoids, neuralgia, migraine headaches, sciatica and ulcers (*5, 8*). Also used as a diuretic, an emmenagogue and an antimalarial agent (*5, 8*).

## Pharmacology

### *Experimental pharmacology*

#### Antidepressant activity

Behavioural studies, performed primarily in rodents, have demonstrated the antidepressant activity of Herba Hyperici by measuring the exploratory and locomotor activities of animals in an unknown environment (*34, 35*). Intragastric administration of a 95% ethanol extract of the herb to male gerbils (2 mg/kg body weight) suppressed clonidine-induced depression. Intragastric administration of the extract to male mice (5 mg/kg body weight) enhanced exploratory activity in a foreign environment and significantly prolonged narcotic-induced sleeping time in a dose-dependent manner; the treated mice also exhibited reserpine antagonism. Similar to standard antidepressant drugs, the extract (6 mg/kg body weight) increased the activity of mice in the waterwheel test following a single dose; prolonged administration (6 mg/kg body weight, daily for 3 weeks) decreased aggressiveness in socially isolated male mice (*35*). Intraperitoneal administration of a 50% ethanol extract of the herb to mice (250 mg/kg body weight) reduced the tail flick response to radiant heat, and significantly decreased swimming time in the forced swimming test ($P < 0.05$) and walking time on a rotating rod ($P < 0.005$), as well as exploratory activity ($P < 0.05$) (*36*). Significant, dose-dependent, antidepressant activities were observed in the behavioural despair test and the learned helplessness paradigm in rats treated intragastrically with a carbon dioxide extract of the crude drug containing 38.8% hyperforin (30 mg/kg body weight) or an ethanol extract containing 4.5% hyperforin (300 mg/kg body weight) ($P < 0.001$). The results were comparable to those obtained following intraperitoneal administration of imipramine (10 mg/kg body weight) (*37*). Intragastric administration of an ethanol extract containing 4.5% hyperforin (50, 150 and 300 mg/kg body weight, daily for 3 days) or a carbon dioxide extract devoid of hypericin but containing 38.8% hyperforin (5, 15 and 30 mg/kg body weight, daily for 3 days) had similar antidepressant activity in rodents (rats and mice) (*38, 39*). In the same dosage range, the ethanol extract potentiated dopaminergic behavioural responses, whereas these effects were either absent or less pronounced in rodents treated with the carbon dioxide extract. In contrast, serotoninergic effects of the carbon dioxide extract were more pronounced than those of the ethanol extract (*38*). Intragastric administration of a methanol extract contain-

ing both hypericin and pseudohypericin (500 mg/kg body weight) to mice produced a dose-dependent increase in ketamine-induced sleeping time and also increased body temperature. The extract also decreased immobility time in the tail suspension test and forced swimming tests, which are both regarded as indicative of antidepressant activity (*40*). Intragastric administration of a 50% ethanol extract of the herb prolonged pentobarbital-induced sleeping time (13.25 mg/kg body weight) and depressed the central nervous system in male mice (25.50 mg/kg body weight). The observed effects were similar to those seen in mice treated with diazepam (2 mg/kg body weight) (*41*). Measurement of some metabolites of biological amines in the urine of various animal models has established a correlation between the excretion in the urine of 3-methoxy-4-hydroxyphenylglycol, the main metabolite of noradrenaline, with the start of the therapeutic antidepressant activity (*42*).

A hydroalcoholic extract of the herb inhibited serotonin (5-hydroxytryptamine, 5-HT) receptor expression in mouse brain synaptosome preparations in vitro (50 μmol/l), and similar effects were observed during ex vivo experiments (*43*). In other studies, hydroalcoholic extracts of the herb inhibited serotonin reuptake ($IC_{50}$ 6.2–25.0 μg/ml) (*44, 45*), and inhibited both γ-aminobutyric acid (GABA) reuptake ($IC_{50}$ 1 μg/ml) and GABA type A receptor binding ($IC_{50}$ 3 μg/ml) in vitro (*46*).

A hydroalcoholic extract of the fresh flowers and buds of *H. perforatum* (containing 0.1% hypericin) was subjected to a series of assays involving 39 receptor types and two enzymes. Receptor assays exhibiting at least 50% radioligand displacement or 50% inhibition of monamine oxidase (MAO) were considered to be active. The extract demonstrated specific affinity for the GABA (types A and B), serotonin, benzodiazepine and inositol triphosphate receptors, non-specific affinity for adenosine receptors and inhibited MAO types A and B. Purified hypericin lacked any significant MAO (type A or B)-inhibitory activity at concentrations up to 10 μmol/l, and had affinity only for *N*-methyl-D-aspartate (NMDA) receptors in rat forebrain membranes (*47*).

An ethanol extract of the herb inhibited radioligand binding to the NMDA, GABA type A and GABA type B receptors ($IC_{50}$ 7.025, 3.240 and 3.310 μg/ml, respectively). The extract also inhibited synaptosomal GABA and L-glutamate uptake in vitro ($IC_{50}$ 1.11 and 21.25 μg/ml, respectively) (*48*).

A methanol or carbon dioxide extract of the herb, and pure hyperforin significantly inhibited synaptosomal uptake of serotonin, noradrenaline, dopamine, L-glutamate and GABA in vitro (*49*). The carbon dioxide extract (containing 38.8% hyperforin) was more active than the methanol extract (containing 4.5% hyperforin), due to the higher hyperforin concentration. Inhibition was most pronounced with purified hyperforin, showing the following order of affinity: noradrenaline ≥ dopamine > GABA ≥ serotonin >> glutamate ($IC_{50}$ 0.043–0.445 μg/ml) (*49, 50*). Neither hyperforin nor the carbon dioxide extract inhibited the activity of MAO type A or B at concentrations up to 50 μg/ml (*49*).

A methanol extract of dried *H. perforatum* flowers inhibited radiolabelled-flumazenil binding to the benzodiazepine sites of the GABA receptor in rat brain

preparations in vitro ($IC_{50}$ 6.83 µg/ml) (*51*). The number of serotonergic 5-$HT_1$ A and 5-$HT_2$ A receptors significantly increased in the brains of rats treated with an ethanol extract of the herb (2.7 g/kg body weight) daily for 26 weeks, whereas the affinity of both serotonergic receptors remained unaltered. These data suggest that prolonged administration of the extract induced upregulation of the 5-$HT_1$ A and 5-$HT_2$ A receptors (*52*). The affinity of hypericin for 30 types of receptor and reuptake sites was determined in vitro. At 1 µmol/l, hypericin inhibited less than 40% specific radioligand binding at all sites tested, except binding at the acetylcholine and sigma receptors (*53*).

The mechanism of the antidepressant effect of Herba Hyperici is not well understood. Early studies focused on the inhibition of MAO and catechol-*O*-methyltransferase (COMT), the two enzymes responsible for the catabolism of biological amines, such as serotonin. Initial investigations analysed the in vitro inhibition of MAO using a series of xanthones isolated from extracts of the herb (*54, 55*). In later studies, hypericin was reported to inhibit MAO type A ($IC_{50}$ $6.8 \times 10^{-5}$ mol/l) and type B ($IC_{50}$ $4.2 \times 10^{-5}$ mol/l) in rat brain mitochondria in vitro (*56*). However, analysis of the hypericin fraction used in these experiments revealed that at least 20% of the extract was composed of other constituents, including some flavonoid derivatives (*8*). Xanthone-containing fractions, free of hypericin and tannins, of a hydroalcoholic extract of *H. perforatum* showed significant inhibition in vitro of MAO type A (which is specific for serotonin) (*57*). In other investigations, only the flavone aglycone, quercitrin, and the xanthone derivative, norethyriol, showed significant inhibition of MAO type A (*57–59*). Hypericin was excluded as the active constituent, and the flavonols and 1,3,6,7-tetrahydroxyxanthone were reported to be the active constituents of a crude extract of the herb (*57–59*). Molecular modelling studies of the constituents of the herb also indicated that the flavonoids may be the most likely candidates for inhibitors of MAO, as their structures are similar to those of known MAO type A inhibitors, toloxotone and brofaromine (*60*).

The MAO-inhibiting activity of six fractions of a hydroalcoholic extract of the herb was determined in vitro and ex vivo. In vitro inhibition of MAO type A in rat brain homogenates could only be shown at a concentration of 1–10 mmol/l of a crude extract or a flavonoid-rich fraction. In ex vivo studies using albino rats, neither the crude extract nor the xanthone-containing fractions inhibited MAO type A or MAO type B after intraperitoneal administration of 300 mg/kg body weight of the extract or 1–10 nmol/l of the fractions. In addition, purified hypericin did not inhibit MAO type A either in vitro or ex vivo (*61*).

The in vitro effects of hypericin, an ethanol extract, and fractions of the extract were tested for inhibition of MAO and COMT obtained from pig liver. Inhibition of MAO was seen with hypericin (1 mmol/l),[1] ethanol extract (0.1 mmol/l),[1] and a fraction containing hypericins and flavonols (0.01 mmol/l).[1]

[1] Molar concentrations were based on a mean molar mass of 500 (*62*).

Weak inhibition of COMT was observed with hypericin and the ethanol extract (both at a concentration of 1 mmol/l),[1] whereas two fractions, containing flavonols and xanthones, inhibited COMT to a greater extent at 0.1 mmol/l[1] (*62*). However, the inhibitory concentrations observed during this study appear to be too high to be of any clinical significance.

Other possible mechanisms of the antidepressant effect of Herba Hyperici include its ability to modulate the production of mediators of inflammation such as cytokines, particularly interleukins. Strong suppression of interleukin-6 (IL-6) release was observed in blood samples from depressed patients treated with *H. perforatum* extract (*63*). IL-6 is involved in the modulation of the hypothalamic–pituitary–adrenal (HPA) axis within the nervous/immune system. Elevated IL-6 levels activate the HPA axis, thus increasing levels of adrenal hormones that play a role in depression.

### Effect on smooth muscle contraction

A 95% ethanol extract or tincture of the herb (200 μg/ml) inhibited barium- and histamine-induced smooth muscle contractions of guinea-pig ileum in vitro (*64*), and contractions of cat and mouse intestine (*65*). An ethyl acetate extract of the herb (0.1 mg/ml) inhibited potassium chloride- and histamine-induced contractions in pig coronary artery in vitro (*66*).

### Antibacterial and antiviral activity

A methanol extract of Herba Hyperici inhibited the growth in vitro of *Escherichia coli*, *Proteus vulgaris*, *Streptococcus mutans*, *Streptococcus sanguis*, *Staphylococcus oxford* and *Staphylococcus aureus (*MIC 0.31–1.25 mg/ml) (*67*). An acetone, hot aqueous or ethyl acetate extract of the herb was active against influenza virus A2 (Mannheim 57), herpes simplex virus 2, poliovirus II and vaccinia virus in vitro (*68*, *69*). However, a decoction or hydroalcoholic extract of *H. perforatum* dried stem was not active against herpes simplex virus 1 or 2, or HIV in vitro (100 μg/ml) (*70*). In vitro activity of hypericin has been demonstrated against Friend murine leukaemia virus, hepatitis B virus, murine cytomegalovirus, human cytomegalovirus (Davis strain), parainfluenza 3 virus, Sindbis virus, vaccinia virus, vesicular stomatitis virus and equine infectious anaemia virus (*71–77*). Hypericin and pseudohypericin also inhibited herpes simplex virus types 1 and 2, and HIV-1 in vitro (*75*, *77–83*). Hypericin inhibited the activity of HIV reverse transcriptase in vitro ($IC_{50}$ 0.77 mmol/l) (*74*, *80*, *84*), and inhibited herpes simplex virus, Rauscher murine leukaemia and Friend murine leukaemia viruses in mice after intravenous, intraperitoneal or intragastric administration (*80–82*). Intraperitoneal administration of a 5% aqueous extract of the herb to mice resulted in viricidal activity against tick-borne encephalitis virus (*85*). Hypericin displayed marginal activity in vitro against Molony murine leukaemia virus and did not show selective activity against herpes simplex

[1] Molar concentrations were based on a mean molar mass of 500 (*62*).

virus, influenza virus A, adenovirus or poliovirus (*82*). However, incubation of the virus with hypericin prior to infection resulted in viricidal activity against all enveloped viruses tested ($IC_{50}$ 1.56–25 µg/ml), but not against non-enveloped viruses (*82*). The antiviral activity of hypericin appears to involve a photoactivation process that forms a singlet oxygen and inactivates both viral fusion and syncytia formation (*72, 75, 86*).

### Protein kinase C inhibition

Numerous in vitro studies have demonstrated that hypericin is a potent inhibitor of protein kinase C (*87–92*). Hypericin treatment of glioma cell lines inhibited growth and also induced cell death due to protein kinase C (*93*). Receptor tyrosine kinase activity of epidermal growth factor is also inhibited by hypericin and may be linked to its antiviral and antineoplastic effects (*89, 94*). The inhibition of protein kinase C may contribute to the anti-inflammatory effects of Herba Hyperici, as hypericin also inhibited the release of arachidonic acid and leukotriene B4 (*94*).

### Wound healing

External application of a 20% aqueous extract of the crude drug to the skin of guinea-pigs and rabbits accelerated healing of experimentally induced wounds (*95, 96*). Intragastric administration of a 60% ethanol extract of the dried leaves to rats (0.1 ml/animal) accelerated healing of experimentally induced wounds by enhancing the strength and rate of wound contraction and epithelialization (*97*).

## *Clinical pharmacology*

### Antidepressant activity

#### *Clinical trials without controls*

The safety and efficacy of oral administration of Herba Hyperici has been assessed in more than 5000 patients in numerous case reports and studies (*22, 23, 31, 98*). In a drug-monitoring study involving 3250 patients, 49% were assessed as being mildly depressed, 46% as moderately depressed and 3% as severely depressed at the beginning of the trial. The patients were treated with 300 mg of a dried 80% methanol extract of the herb three times daily, and evaluated after 2 and 4 weeks of therapy. After treatment, 80% of patients had improved or were symptom-free, while 13–16% remained unchanged or were worse. Minor adverse reactions were reported in 2.4% of patients (*31*). A post-marketing trial was performed with 2404 patients with symptoms of mild to moderate depression who were treated with 2–4 capsules of an ethanol extract of the herb (equivalent to 0.6–1.8 mg total hypericin) daily for 4–6 weeks. Symptomatic improvement was evaluated as good to very good in 77% of patients and satisfactory in 15% (*99*).

The effects of an ethanol extract of the herb on the electroencephalogram (EEG) of 40 patients with depression were determined following administra-

tion of the extract (equivalent to 0.5 mg total hypericin or 1.4 g crude drug) daily for 4 weeks. An increase in theta-activity, a decrease in alpha-activity and no change in beta-activity were observed, indicating the induction of relaxation (*100*). A significant increase in nocturnal melatonin plasma concentration was observed in 13 healthy subjects treated with a hydroethanolic extract of the herb (equivalent to 0.53 mg total hypericin) daily for 3 weeks (*101*). A significant increase in the concentration of neurotransmitters in the urine was observed 2 hours after administration of a standardized ethanol extract of the crude drug to six women with symptoms of depression (*42*).

### *Reviews of clinical trials*

The results from over 28 controlled clinical trials involving oral administration of Herba Hyperici have been published. Twelve of the trials, involving 950 patients, were conducted using an ethanol extract of the herb, while the other 16 trials of 1170 patients used a dried 80% methanol extract (*26*). A systematic review and meta-analysis of 23 of the randomized clinical trials involving 1757 patients assessed the efficacy of the herb in the symptomatic treatment of mild to moderate depression. Twenty trials were double-blind, one was single-blind and two were open studies. Fifteen of the trials involving 1008 patients were placebo-controlled and eight studies of 749 patients were comparison trials with other antidepressant drugs. With the exception of two trials, all studies had treatment periods of 4–8 weeks. The daily dosage ranged from 0.4 to 2.7 mg hypericin in 300–1000 mg of a standardized extract of the herb. Seventeen trials used the Hamilton Rating Scale for Depression (Hamilton Depression Rating Scale), which focuses primarily on somatic symptoms, to measure effectiveness, while 12 trials used the Clinical Global Impression Scale. The latter involves observer-rated analysis of severity of illness, global improvement and efficacy. The meta-analysis concluded that the herb was significantly superior to the placebo and was as effective as standard antidepressants such as maprotiline or imipramine (75 mg three times daily). Fewer side-effects were seen in the herb-treated patients (19.8%) than in those receiving standard antidepressants (52.8%) (*21*).

A systematic, criteria-based review of 18 controlled clinical trials using either ethanol or methanol extracts of the herb as a treatment for depression was carried out. Twelve of the trials (nine placebo-controlled and three comparison trials) met the methodological inclusion criteria and were included in the review. The results of the cumulative data show that extracts of the herb were superior to the placebo for the symptomatic treatment of depression as measured by the Hamilton Depression Rating Scale. Results of the comparison studies with maprotiline (75 mg daily) and imipramine (50–75 mg daily) and other standard antidepressants suggest that extracts of the herb have a similar therapeutic profile. Some flaws in the reported studies included no intention to treat analysis, lack of control over compliance, and insufficient description of the extract or placebo used (*19*).

A review of 12 double-blind, placebo-controlled and three comparison clinical trials assessed the efficacy of the herb for the treatment of mild to moderate depression, and the methodology used to perform the studies. The review concluded that the antidepressant activity of a standardized extract of the herb (300 mg standardized to contain 0.9 mg hypericin three times daily for 4–8 weeks) was sufficiently documented. However, it also concluded that no dose-finding studies had been conducted, and that studies on inpatients with severe depression and endogenously depressed patients were lacking. In the three comparison studies, the daily dose of 75 mg maprotiline or 30 mg amitriptyline was viewed as too low. The review concluded that further trials of longer duration in comparison with higher doses of standard antidepressants are warranted (*27*).

A double-blind, randomized, multicentre study was performed to evaluate the efficacy, safety and tolerability of a daily dose of 900 mg hydroalcoholic extract of the herb or 75 mg amitriptyline. After a 1-week placebo run-in phase, 156 patients were treated with 300 mg extract or 25 mg amitriptyline, three times daily for 6 weeks. The patients were assessed before and after treatment. The Hamilton Depression Rating Scale changed from 20 to 10 in the extract-treated patients and from 21 to 6 in the amitriptyline-treated patients ($P < 0.05$). The Montgomery-Asberg Rating Scale for Depression changed from 27 to 13 in the extract-treated patients, and from 26 to 6.5 in the amitriptyline-treated patients ($P < 0.05$). Similar scores in the Clinical Global Impression Scale were observed in both groups (*29*). In a randomized, double-blind, multicentre trial the effectiveness of a standardized dried 80% methanol extract of the herb (containing 0.3% hypericin) was compared with that of imipramine in 209 patients with recurrent depressive disorder, current episode severe without psychotic symptoms (*18*). Patients were treated daily with 1800 mg extract or 150 mg imipramine for 6 weeks. Assessment of patients before and after treatment revealed the following changes. In the Hamilton Depression Rating Scale: from 25.3 to 14.4 in the extract-treated patients, and from 26.1 to 13.4 in the imipramine-treated patients ($P < 0.021$). In the von Zerssen Depression Scale: from 28.9 to 13.6 in the extract-treated patients, and from 26 to 6.5 in the imipramine-treated patients ($P < 0.05$). Results in the Clinical Global Impression Scale showed a trend in favour of imipramine. Although the efficacy of the extract was not significantly different from that of imipramine, analysis of the patient subgroups showed that it was most effective in patients with moderately severe depression (*28*).

A prospective, randomized, double-blind, placebo-controlled, multicentre study assessed the safety and efficacy of a standardized ethanol extract of the herb for the treatment of 151 patients with mild and moderate depressive episodes (classified as F32.0 and F32.1, respectively, in 1CD-10 (*18*)). Patients received either one 250 mg tablet of the extract (equivalent to 1 mg hypericin) or a placebo twice daily for 6 weeks. The primary efficacy variable was the Hamilton Depression Rating Scale, and secondary variables were the risk–benefit Clinical Global Impression Scales I–III and Visual Analogue Scale

(a validated, patient self-assessment test). Decreases were seen in the Hamilton Depression Rating Scale in 56% of patients treated with the extract, whereas decreases were seen in only 15% of patients who received the placebo (*24*). A randomized, double-blind, placebo-controlled, multicentre study assessed the clinical efficacy and safety of two extracts of the herb differing in their hyperforin content (0.5% or 5.0% hyperforin) in 147 patients suffering from mild to moderate depression as classified in the *Diagnostic and statistical manual of mental disorders*, 4th ed. (DSM-IV) of the American Psychiatric Association (*102*). The patients received either 900 mg of one of the extracts or a placebo daily for 42 days. The patients who received the extract containing 5% hyperforin showed the largest decrease in the Hamilton Depression Rating Scale (a reduction of 10.3; $P = 0.004$, compared to the placebo). A reduction of 8.5 following treatment with the extract containing 0.5% hyperforin and of 7.9 in the placebo-treated group was seen (*20*).

In a double-blind, placebo-controlled, crossover study, 12 healthy volunteers treated with a dried hydromethanolic extract of the herb (300 mg three times daily for 4 weeks) showed improved sleep quality with an increase in deep-sleep phases (*25*). A randomized, double-blind, placebo-controlled study of 54 healthy volunteers evaluated the central pharmacodynamic effects of two extracts of the herb with different hyperforin contents (0.5% or 5.0%) but identical hypericin content. Healthy volunteers received either 900 mg (300 mg three times daily) of one of the extracts or a placebo daily for 8 days. A quantitative topographic electroencephalogram (qEEG) was performed on days 1 and 8 as an indicator of drug-induced pharmacological activity. In both treatment groups, reproducible central pharmacodynamic effects were observed between 4 and 8 hours after administration, and were confirmed on day 8. The extract containing 5% hyperforin showed a marked tendency to produce greater increases in qEEG baseline power performances than the extract containing 0.5% hyperforin. Higher baseline outputs were observed on day 8 in the delta-, theta- and alpha-1 frequencies. Patients treated with the extract containing 5% hyperforin had an increase in qEEG power performance in the delta-frequency after a single dose and in the theta- and alpha-1 frequencies after 8 days of treatment, when compared with placebo treatment (*103*).

In a double-blind, placebo-controlled, crossover study, 12 healthy volunteers were treated with 900 mg (300 mg three times daily) of a dried hydromethanolic extract of the herb for 6 weeks, and the effects on the EEG were assessed. A reduction in alpha-activity and audiovisual latencies in evoked potentials and an increase in beta- and theta-activities were demonstrated (*104*). Another randomized, double-blind, clinical trial of 24 healthy volunteers compared the effects of a dried hydromethanolic extract of the herb with those of maprotiline on the resting EEG and audio-visual latencies in evoked potentials. After 4 weeks of treatment, an increase in theta- and beta-2 activity was observed in patients treated with 900 mg of a standardized hydroalcoholic extract (300 mg three times daily), while a decrease in theta-activity was seen in patients treated with 30 mg maprotiline (10 mg three times

daily) (*105*). The extract also induced an increase of deep sleep as demonstrated by visual analysis of the sleeping phases and automatic analysis of slow-wave EEG activities. Rapid eye movement sleep was not influenced (*25*).

A randomized, single-blind study evaluated the efficacy of the herb for the treatment of seasonal affective disorders (SAD) in conjunction with light therapy. Twenty patients with SAD were treated with 900 mg (300 mg three times daily) of a hydroalcoholic extract of the herb daily for 4 weeks, combined with either bright (3000 lux) or dim light (<300 lux) conditions. Light therapy was carried out for 2 hours daily. A significant reduction of the Hamilton Depression Rating Scale in both groups, but no statistically significant difference between the two groups, was observed (*106, 107*).

### Photodynamic effects

The photodynamic effects of hypericin, incorporated into a non-ionic hydrophilic ointment base, were assessed after external application to the skin of patients with herpes communis. The infected dermal surface of treated patients recovered rapidly and the effects lasted in most cases (*33*).

### Pharmacokinetics

Single-dose pharmacokinetics of hypericin and pseudohypericin were determined in 12 healthy male volunteers. After a single dose of 300, 900 or 1800 mg extract (equivalent to 250, 750 or 1500 μg hypericin, respectively, and 526, 1578 or 3156 μg pseudohypericin, respectively), plasma levels of the hypericins were measured by high-performance liquid chromatography for up to 3 days. The median plasma levels were 1.5, 4.1 and 14.2 ng/ml for hypericin, and 2.7, 11.7 and 30.6 ng/ml for pseudohypericin, for the three stated doses, respectively. The median half-life of hypericin was 24.8–26.5 hours and 16.3–36.0 hours for pseudohypericin. The median lag-time of absorption was 2.0–2.6 hours for hypericin and 0.3–1.1 hours for pseudohypericin. During long-term dosing (900 mg daily), a steady state was reached after 4 days. The mean maximum plasma level during the steady state was 8.5 ng/ml for hypericin and 5.8 ng/ml for pseudohypericin (*108*).

A randomized, placebo-controlled clinical trial was performed to evaluate the pharmacokinetics and dermal photosensitivity of hypericin and pseudohypericin in 13 healthy volunteers after administration of a single dose of either a placebo or 900, 1800 or 3600 mg of the extract (equivalent to 0.00, 2.81, 5.62 and 11.25 mg total hypericin [combined hypericin and pseudohypericin], respectively). The maximum total hypericin plasma levels observed at 4 hours after administration were 0, 28, 61 and 159 ng/l, respectively. Before and 4 hours after drug intake, the subjects were exposed to increasing doses of solar-simulated irradiation on small areas of their backs. No dose-related increase in light sensitivity was observed. In the multiple-dose analysis, 50 healthy volunteers received 600 mg extract of the herb three times during 1 day only. A slight increase in solar-simulated irradiation sensitivity was observed (*109*).

In a randomized, four-way crossover study without controls involving six healthy volunteers, the pharmacokinetics of hyperforin were determined after administration of single doses of 300, 600, 900 or 1200 mg of an alcohol extract containing 5% hyperforin. The maximum plasma level of hyperforin (150 ng/ml) was reached 3.5 hours after administration of 300 mg of the extract. The hyperforin half-life and mean residence time were 9 and 12 hours, respectively. The pharmacokinetics were linear up to 600 mg of the extract. Increasing the dose to 900 or 1200 mg of extract resulted in values for maximum clearance and area under the curve lower than those expected from linear extrapolation of data from the lower doses (*110*). The pharmacokinetics of hyperforin were studied in nine healthy volunteers, as part of a double-blind, randomized, placebo-controlled study of 54 subjects. The subjects received either a single dose of 900 mg of an alcohol extract containing 5% hyperforin, or 300 mg of an alcohol extract containing 5% hyperforin three times daily for 8 days. No accumulation of hyperforin in the plasma was observed. On the basis of the area under the curve values from the multiple-dose study, the estimated steady-state plasma concentration of hyperforin was approximately 100 ng/ml (*110*).

## Contraindications

Herba Hyperici is contraindicated in cases of known allergy to plants of the Clusiaceae family.

## Warnings

As with other antidepressant drugs, observation of the therapeutic effects of Herba Hyperici may require 2–4 weeks of therapy. If a significant antidepressant effect is not observed after 6 weeks of treatment, a physician should be consulted.

## Precautions

### *General*

Ultraviolet treatments or prolonged exposure to direct sunlight should be avoided when Herba Hyperici is used, as photosensitization may occur in light-sensitive individuals (*32*). (See Adverse reactions.)

### *Drug interactions*

Although the ingestion of foods containing high concentrations of tyramine such as pickled or smoked foods and cheese, and selective serotonin reuptake inhibitors such as fluoxetine are contraindicated with MAO inhibitors, in vivo data linking Herba Hyperici to MAO inhibition are lacking (*111*, *112*). The com-

bination of Herba Hyperici with other standard antidepressant drugs, such as tricyclic antidepressants or fluoxetine, is not recommended, unless under medical supervision.

There are now numerous reports in the medical literature indicating that Herba Hyperici extracts induce hepatic enzymes that are responsible for drug metabolism and may reduce the serum levels and therapeutic efficacy of drugs (*113–117*). Coadministration of theophylline with a Herba Hyperici extract lowered the serum level of theophylline in a patient previously stabilized, requiring an increase in the theophylline dose (*113*). Coadministration of Herba Hyperici and digoxin reduced serum digoxin concentrations after 10 days of treatment (*114*). A decrease in serum cyclosporin, warfarin and phenprocoumon concentrations was seen in patients after they had additionally taken Herba Hyperici extracts (*115*). Concomitant use of Herba Hyperici in five patients previously stabilized on serotonin-reuptake inhibitors resulted in symptoms of central serotonin excess (*116*). The United States Food and Drug Administration has publicized a report concerning a significant drug interaction between Herba Hyperici and indinavir, a protease inhibitor used to treat HIV infections (*117*). Herba Hyperici substantially reduced indinavir plasma concentrations, due to induction of the cytochrome P450 metabolic pathway. As a consequence, the concomitant use of Herba Hyperici and protease inhibitors or non-nucleoside reverse transcriptase inhibitors is not recommended and may result in suboptimal antiretroviral drug concentrations, leading to a loss of virucidal activity and the development of resistance (*117*).

### Carcinogenesis, mutagenesis, impairment of fertility

The mutagenicity of hydroalcoholic extracts of Herba Hyperici containing 0.2–0.3% hypericin and 0.35 mg/g quercetin has been studied in various in vitro and in vivo systems (*118–121*). The in vitro studies were performed using the *Salmonella*/microsome assay, hypoxanthine guanidine phosphoribosyl transferase test (up to 4 µl/ml), unscheduled DNA synthesis test (up to 1.37 µl/ml), cell transformation test in Syrian hamster embryo cells (up to 10 µl/ml) and spot test in mice (up to 10 µl/ml). The in vivo tests included the chromosome aberration test with bone marrow cells of Chinese hamsters (10 ml/kg body weight, gastric lavage) and the micronucleus test in rodent bone marrow (2 g/kg body weight, gastric lavage). Although some positive results were observed in vitro in the *Salmonella*/microsome assay (*119*, *121*), all the in vivo tests were negative, indicating that the hydroalcoholic extract was not mutagenic in animals. In a 26-week study, intragastric administration of the hydroalcoholic extract to rats and dogs (900 and 2700 mg/kg body weight) had no effect on fertility, development of the embryo, or pre- or postnatal development (*122*).

### Other precautions

No information available on precautions concerning drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; nursing

mothers; or paediatric use. Therefore, Herba Hyperici should not be administered during pregnancy or lactation or to children without medical supervision.

## Adverse reactions

Phototoxicity has been reported in cattle after ingestion of *H. perforatum* during grazing. However, the doses were estimated to be approximately 30–50 times higher than normal therapeutic doses (*123*). Photosensitization in light-sensitive individuals has been demonstrated in a controlled clinical trial involving metered doses of hypericin and exposure to ultraviolet A and B irradiation. Patients were treated with 600 mg of a hydroalcoholic extract of the herb (containing 0.24–0.32% total hypericin) three times daily for 15 days. A measurable increase in erythema in light-sensitive individuals was observed after ultraviolet A irradiation. The plasma concentration of hypericin and pseudohypericin in these subjects was double that seen during normal therapeutic treatment of depression (*124*). A single case of reversible erythema after exposure to ultraviolet B has been reported in one patient who had been taking the herb for 3 years (*125*). A single case of acute neuropathy after exposure to sunlight has been reported in one patient taking the herb (*126*). Drug-monitoring studies indicate that side-effects of the herb are rare and mild, and include minor gastrointestinal irritations, allergic reactions, tiredness and restlessness. However, these studies did not last longer than 8 weeks (*21*, *24*, *31*). Clinical studies have suggested that the use of the herb does not affect general performance or the ability to drive (*127*, *128*).

## Dosage forms

Dried crude drug for decoction, powdered drug or extracts in capsules, tablets, tinctures and drops (*2*, *7*, *32*). Topical preparations include the oil, infusions, compresses, gels and ointments. Store in a well-closed container, protected from light (*10*, *11*).

## Posology

(Unless otherwise indicated)

Daily dosage: 2–4 g crude drug (*32*). Internal use: standardized tinctures or fluidextracts (*23*, *98*, *100*), or standardized hydroethanolic or dried hydromethanolic extracts, up to a daily dose of 900 mg extract (equivalent to 0.2–2.7 mg total hypericin) (*19*, *21*, *22*, *27*, *31*).

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# Aetheroleum Melaleucae Alternifoliae

## Definition

Aetheroleum Melaleucae Alternifoliae is the essential oil obtained by steam distillation of the leaves and terminal branchlets of *Melaleuca alternifolia* (Maiden and Betche) Cheel (Myrtaceae) (*1–3*).

## Synonyms

No information available.

## Selected vernacular names

Australian tea tree, tea tree (*1–5*).

## Geographical distribution

Indigenous to Australia, where it is grown commercially (*6*, *7*).

## Description

A narrow-leaved tree not exceeding 6 m. Entire plant glabrous; leaves alternate. Flowers scattered in an interrupted spike; stamens more than 12 mm long united at their bases to form 5 distinct bundles; capsule persisting within fruiting hypanthium (*6–8*).

## Plant material of interest: essential oil

### *General appearance*

A colourless to pale-yellow liquid (*1–3*).

### *Organoleptic properties*

Odour: myristic (*1*, *2*).

### *Microscopic characteristics*

Not applicable.

### *Powdered plant material*
Not applicable.

## General identity tests
Physico-chemical properties, thin-layer and gas chromatography (*1*, *2*).

## Purity tests
### *Microbiological*
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*9*).

### *Chemical*
Refractive index: 1.475–1.482 (*1–3*);
Optical rotation: +5° to +15° (*1–3*);
Relative density: 0.885–0.906 (*1–3*);
Solubility in alcohol: soluble in two volumes of 85% ethanol at 20°C (*1–3*).

### *Pesticide residues*
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*10*). For other pesticides, see the *European pharmacopoeia* (*10*), and the WHO guidelines on quality control methods for medicinal plants (*9*) and pesticide residues (*11*).

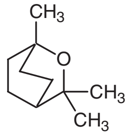
### *Heavy metals*
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*9*).

### *Radioactive residues*
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*9*) for the analysis of radioactive isotopes.

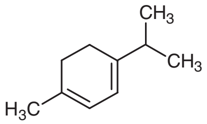
### *Chemical assays*
Contains not less than 30% (w/w) of terpinen-4-ol (4-terpineol) and not more than 15% (w/w) of 1,8-cineole (also known as cineol, cineole or eucalyptol) (*1*, *2*). The oil must contain: not less than 3.5% sabine; 1–6% α-terpinene; 10–28% γ-terpinene; 0.5–12.0% *p*-cymene; not less than 30% terpinen-4-ol; and 1.5–8.0% α-terpineol, as measured by gas chromatography (*1–3*).

## Major chemical constituents
The major constituents are terpinen-4-ol (29–45%), γ-terpinene (10–28%), α-terpinene (2.7–13.0%) and 1,8-cineole (4.5–16.5%) (*8*, *12–15*). Other mono-

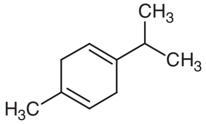
terpenes present in significant quantities (1–5%) include α-pinene, limonene, *p*-cymene and terpinolene. The structures of the major monoterpenes are presented below.



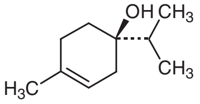
1,8-cineole (eucalyptol)



α-terpinene



γ-terpinene



and enantiomer terpinen-4-ol (4-terpineol)

# Medicinal uses

## Uses supported by clinical data

Topical application for symptomatic treatment of common skin disorders such as acne, tinea pedis, bromidrosis, furunculosis, and mycotic onychia (onychomycosis), and of vaginitis due to *Trichomonas vaginalis* or *Candida albicans*, cystitis and cervicitis (*16–23*).

## Uses described in pharmacopoeias and in traditional systems of medicine

As an antiseptic and disinfectant for the treatment of wounds (*5*).

## Uses described in folk medicine, not supported by experimental or clinical data

Symptomatic treatment of burns, colitis, coughs and colds, gingivitis, impetigo, nasopharyngitis, psoriasis, sinus congestion, stomatitis and tonsillitis (*24*, *25*).

# Pharmacology

## Experimental pharmacology

### Antimicrobial activity

Aetheroleum Melaleucae Alternifoliae inhibited the growth in vitro of *Escherichia coli*, vancomycin-resistant *Enterococcus faecium*, *Staphylococcus aureus*, metacillin-resistant *Staphylococcus aureus*, and a variety of *Streptomyces* species (MIC 0.04–0.50%) (*26–30*). It also inhibited the growth in vitro of *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum canis*, *Malassezia furfur*, *Candida albicans*, *Cryptococcus neoformans*, *Pityrospermum ovale* and *Trichosporon cutaneum* (MIC 1.1–2.2 mg/ml) (*31–35*). The susceptibility of 32 strains of *Propionibacterium acnes* to the essential oil was determined using a broth dilution method. The MIC was 0.25% for five strains, and 0.50% for the other strains (*36*). Several chemical constituents of the oil, linalool, terpinen-4-ol, α-terpineol,

α-terpinene, terpinolene and 1,8-cineole, inhibited the growth in vitro of a wide variety of microorganisms, including *Candida albicans*, *Escherichia coli* and *Staphylococcus aureus* (MIC 0.06–0.50% v/v) (*27*).

### Toxicology

The dermal median lethal dose ($LD_{50}$) of the essential oil in rabbits is >5.0 mg/kg body weight, since 5.0 mg/kg resulted in the deaths of two out of 10 treated rabbits (*37*). The oral $LD_{50}$ in rats is 1.9 g/kg body weight (range of doses 1.4–2.7 g/kg) (*24, 25, 37, 38*). The signs of severe toxicity are respiratory distress, and coma with diarrhoea (*26, 38*). A few cases of toxicosis after topical application of high doses of the essential oil to dogs and cats have been reported. Symptoms included central nervous system depression, weakness, and lack of coordination and muscle tremors that were resolved within 2–3 days after supportive treatment (*39*).

## *Clinical pharmacology*

### Vaginitis and cervicitis

A study without controls assessed the safety and efficacy of a 40% emulsified solution of Aetheroleum Melaleucae Alternifoliae in 13% isopropyl alcohol in the treatment of 130 women with cervicitis or vaginitis due to *Trichomonas vaginalis* or vaginitis due to *Candida albicans*. Intravaginal application of tampons saturated with a 20% emulsified solution healed cervicitis due to *Trichomonas vaginalis* after four weekly treatments. In patients with vaginitis due to *Trichomonas vaginalis*, intravaginal application of a 1% emulsified solution using a saturated tampon, as well as vaginal douching, resulted in clinical cures and restoration of the cervix (*21*). In another study without controls, 28 women with vaginitis due to *Candida albicans* were treated with vaginal pessaries (containing 0.2 g essential oil) every night for 90 days. After 30 days of treatment, 24 patients were already free of symptoms such as leukorrhoea and burning sensation, and 21 were free of *Candida albicans* (*17*).

### Cystitis

A randomized, double-blind, placebo-controlled trial assessed the efficacy of the essential oil in the treatment of 26 women with chronic ideopathic colibacilli cystitis. Patients were treated with 8 mg essential oil, in an enteric capsule form, orally three times daily for 6 months. After treatment, 54% of the essential oil-treated group were free of symptoms, compared with only 15% in the placebo group. However, approximately 50% of the asymptomatic patients still showed evidence of colibacilli and leukocytes in their urine (*17*).

### Acne

A randomized, single-blind, comparison trial evaluated the safety and efficacy of topical application of a gel containing either 5% essential oil or 5% benzoyl

peroxide in the treatment of mild to moderate acne in 119 patients. The results demonstrated that both preparations significantly reduced the number of inflamed and non-inflamed lesions (open and closed comedones) after 3 months of daily treatment ($P < 0.001$), although the onset of action of the gel containing the essential oil was slower than that of the gel containing benzoyl peroxide. Patients treated with the oil-containing gel reported fewer side-effects than those treated with the benzoyl peroxide-containing gel (*16*).

### Foot problems

A randomized double-blind, placebo-controlled clinical trial evaluated the efficacy of a cream containing either 10% (w/w) essential oil, 1% tolnaftate or a placebo in the treatment of 104 patients with tinea pedis due to *Trichophyton rubrum*, *T. mentagrophytes* and *Epidermophyton floccosum*. After application of the cream twice daily for 4 weeks, 30% of the essential oil-treated patients, 85% of the tolnaftate-treated patients and 21% of the placebo-treated patients showed conversion to a negative culture ($P < 0.001$). Both the essential oil-treated group and tolnaftate-treated group demonstrated significant improvement in the clinical symptoms of scaling, inflammation, itching and burning sensation, compared with the placebo group ($P < 0.001$). The cream containing the essential oil reduced symptomatology of tinea pedis as effectively as that containing tolnaftate, but was no better than the placebo in achieving a mycological cure (*22*). A study without controls assessed the efficacy of three products in the treatment of 60 patients with tinea pedis due to *Trichophyton rubrum*, *T. mentagrophytes* and *Epidermophyton floccosum*, as well as other conditions such as bromidrosis, inflamed corns, calluses, bunions, fissures and mycotic onychia (onychomycosis) of the toenails. Eight patients were treated with 100% essential oil, 40 patients were treated with a 40% emulsified solution of the essential oil in 13% isopropyl alcohol and 12 were treated with an ointment containing 8% essential oil, twice daily for 3 weeks to 4 years. The 100% essential oil was assessed as fair to poor in the treatment of mycotic onychia. The 40% emulsified solution reduced the symptoms of bromidrosis, and inflammation of corns, calluses and bunions. The 8% ointment was effective in the symptomatic treatment of tinea pedis due to *T. mentagrophytes* and *Epidermophyton floccosum*, but was less effective against *T. rubrum* (*23*).

A randomized, double-blind, multicentre comparison trial assessed the efficacy of 100% essential oil or 1% clotrimazole in the treatment of 117 patients with distal subungual mycotic onychia. Patients received twice-daily applications for 6 months, and debridement and clinical assessment were performed at 0, 1, 3 and 6 months. After 3 months, approximately 50% of each group reported improvements. After 6 months, clinical assessment showed partial or full resolution in approximately 60% of each group (*19*).

The efficacy of the essential oil was assessed in an open study of 35 patients with furuncles on the axilla, back, ear, face, forearm, neck and scalp. The furuncles were painted with the essential oil two or three times daily, after thorough

cleaning. In the group treated with the essential oil, only one furuncle required incision, and in 15 patients, the furuncles were completely cured after 8 days of treatment. The only adverse reaction was slight temporary stinging reported by three patients. In the untreated control group, furuncles on five of the 10 patients required incision and the infected site of the furuncles was still apparent after 8 days (*20*).

## Contraindications

Aetheroleum Melaleucae Alternifoliae is contraindicated in cases of known allergy to plants of the Myrtaceae family.

## Warnings

Not for internal use. Keep out of reach of children (see Adverse reactions).

## Precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Aetheroleum Melaleucae Alternifoliae should not be administered during pregnancy or lactation or to children without medical supervision.

## Adverse reactions

Allergic contact dermatitis after external application and ingestion of Aetheroleum Melaleucae Alternifoliae has been reported (*26*, *40–44*). No adverse reactions were reported in two patch tests using preparations containing up to 5% essential oil (*45*, *46*). Accidental ingestion of 10 ml essential oil caused confusion, disorientation and loss of coordination in a 23-month-old child (*47*). Ingestion of 2.5 ml essential oil by a 60-year-old man resulted in a severe rash and a general feeling of malaise (*48*). Induction of a comatose state lasting 12 hours, followed by 36 hours of a semi-conscious state accompanied by hallucinations, was reported in one patient after ingestion of approximately half a cup (120 ml) of the essential oil. Abdominal pain and diarrhoea lasting up to 6 weeks were also reported (*38*).

## Dosage forms

Essential oil (*1*, *2*). Store in a well-filled, airtight container, protected from heat and light.

## Posology

(Unless otherwise indicated)

External application of the essential oil at concentrations of 5–100%, depending on the skin disorder being treated (*16–23*).

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# Folium Melissae

## Definition

Folium Melissae consists of the dried leaves of *Melissa officinalis* L. (Lamiaceae, Labiatae) (*1*, *2*).

## Synonyms

*Calamintha officinalis* Moench. (3), *Melissa graveolens* Host, *Thymus melissa* E.H.L. Krause (*4*). Lamiaceae is also referred to as Labiatae.

## Selected vernacular names

Alahana, appiastro, badarendjabouya, badranjbuyeh, balm, balm mint, bee balm, blue balm, cedronella, citromfülevél, citronelle, citrounado, citrounela, citrounelo, common balm, cure-all, dropsy plant, erva-cidreira-miuda-de-folha, folia citronellae, franjmeshk, garden-balm, Herzkraut, hhashyshat ennahhl, honey plant, lemon balm, limiera, limouna, limounneta, mallisa, melissa, Melisse, Melissenblätter, Melissenkraut, melisso, melliss, ponciarada, pouncinado, sidrunmeliss, sweet balm, toronjil, toronjil-cidrado, touroudjan, turungan, Zitronenkraut, Zitronenmelisse (*4*–*8*).

## Geographical distribution

Indigenous to western Asia and the eastern Mediterranean region, and is cultivated in central, eastern and western Europe, and the United States of America (*4*, *7*, *8*).

## Description

An odorous perennial herb, 0.3–0.9 m high, usually with several stems, lemon-scented on bruising. Stems obtusely quadrangular, furrowed pubescent. Leaves 2–9 cm long and 1–5 cm wide, ovate to obovate-oval, base cuneate truncate or cordate at the base, densely pilose on both surfaces, petiole 0.2–3.5 cm long. Corolla white or pinkish; infundibuliform tube 8–12 mm long; stamens inserted deep in the tube; bracteoles oval-oblong, about 1.5 cm long, pubescent; calyx 5–9 mm long, pubescent outside, pubescent inside (with very short hairs), densely pilose in the middle (*4*, *8*, *9*).

## Plant material of interest: dried leaves

### *General appearance*

Leaves oval, cordate, up to about 8 cm long and 5 cm wide, with more or less long petioles; lamina thin, lower surface has conspicuous, raised, reticulate venation; margins roughly dentate or crenate; upper surface bright green, lower surface lighter in colour (*1*).

### *Organoleptic properties*

Odour: aromatic, lemon-like; taste: aromatic, lemon-like (*1*).

### *Microscopic characteristics*

Dorsoventral epidermal cells with sinuous walls and diacytic stomata on lower surface only; very short, conical, unicellular covering trichomes with a finely striated cuticle occur abundantly, especially over the veins on the lower surface; also uniseriate, multicellular (2–5 cells) covering trichomes, wide at the base and narrowing rapidly toward the tip, with slightly thickened, warty walls; secretory trichomes also very abundant, some small with unicellular stalk and unicellular or bicellular head, others large, of laminaceous type, with unicellular stalk and spherical to ovoid head composed of 8 cells (*5*).

### *Powdered plant material*

Greenish. Fragments of the leaf epidermis with sinuous walls; short, conical, unicellular covering trichomes with a finely striated cuticle; uniseriate, multicellular covering trichomes; 8-celled secretory trichomes of laminaceous type, others with unicellular to tricellular stalks and unicellular or, more rarely, bicellular heads; diacytic stomata, on the lower surface only (*1*).

## General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for rosmarinic, chlorogenic and caffeic acids (*1*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

### *Foreign organic matter*

Not more than 2% total foreign matter and not more than 10% of stem fragments with a diameter greater than 1 mm (*1*).

### *Total ash*
Not more than 12% (*1*).

### *Loss on drying*
Not more than 10% (*1*).

### *Pesticide residues*
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

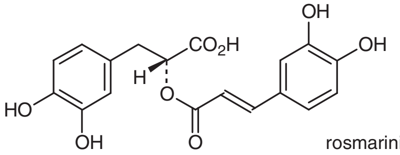
### *Heavy metals*
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

### *Radioactive residues*
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

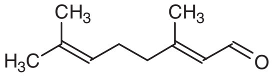
### *Other purity tests*
Chemical, acid-insoluble ash, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

## Chemical assays
Contains not less than 4.0% total hydroxycinnamic acids calculated as rosmarinic acid (*1*). Quantitative analysis is performed by spectrophotometry at 505 nm (*1*). Essential oil analysis is carried out according to the method described in the *European pharmacopoeia* (*1*).

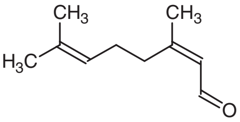
## Major chemical constituents
The major characteristic constituents are the hydroxycinnamic acids (rosmarinic [up to 6%], *p*-coumaric, caffeic and chlorogenic acids), and an essential oil (0.02–0.37%) composed of more than 40% monoterpenes and more than 35% sesquiterpenes. The most significant terpenoid components are citral (a mixture of the isomers neral and geranial), citronellal, geraniol, nerol, linalool, farnesyl acetate, humulene (α-caryophyllene), β-caryophyllene and eremophilene. Other constituents include flavonoids, tannins and acidic triterpenes (e.g. ursolic and oleanolic acids) (*4, 6, 7, 13–15*). The structures of the major compound, rosmarinic acid, and terpenoid components are presented below.



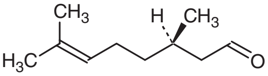
rosmarinic acid



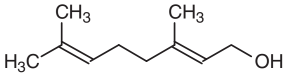
geranial



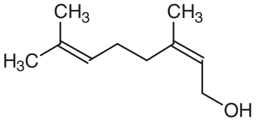
neral



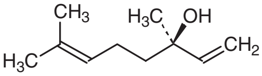
and enantiomer
citronellal



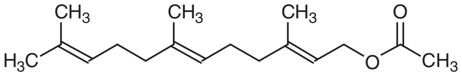
geraniol



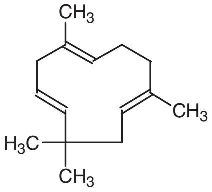
nerol



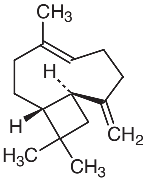
and enantiomer
linalool



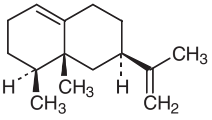
farnesyl acetate



humulene
(α-caryophyllene)



β-caryophyllene



eremophilene

# Medicinal uses

## *Uses supported by clinical data*

Externally, for symptomatic treatment of herpes labialis (*16–18*).

## *Uses described in pharmacopoeias and in traditional systems of medicine*

Orally as a carminative for gastrointestinal disorders, and as a sedative for treatment of nervous disturbances of sleep (*5, 15*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of amenorrhoea, asthma, bee stings, coughs, dizziness, dysmenorrhoea, migraine headaches, tachycardia, toothache, tracheobronchitis and urinary incontinence (*6*, *19*).

## Pharmacology

### *Experimental pharmacology*

#### Antiviral activity

Aqueous extracts of Folium Melissae inhibited the replication in vitro of herpes simplex virus type 2, influenza virus $A_2$ (Mannheim 57) and vaccinia virus at a concentration of 10% (*20*). A dried aqueous extract of the leaves inhibited the replication of herpes simplex viruses in vitro at a concentration of 200 µg/ml (*18*). A condensed tannin isolated from an aqueous extract of the leaves inhibited haemagglutination induced by Newcastle disease virus or mumps virus; protected eggs and chick cell cultures from infection by Newcastle disease virus; and prevented haemagglutination by Newcastle disease, mumps and parainfluenza viruses 1, 2 and 3, but not by influenza viruses A and B (*21*). A tannin-free polyphenol fraction of an aqueous extract of the leaves was active against herpes simplex and vaccinia viruses in egg and cell culture systems (*22*). Aqueous extracts of the leaves have also been reported to have activity against Semliki Forest virus, influenza viruses and myxoviruses in vitro (*23*, *24*).

#### Antispasmodic activity

An ethanol extract of the leaves inhibited histamine- and barium-induced contractions of guinea-pig ileum in vitro (200 µg/ml), while an aqueous extract was inactive (*25*). A 30% ethanol extract did not inhibit acetylcholine- and histamine-induced contractions in guinea-pig ileum in vitro at concentrations up to 10 µl/ml (*26*). The essential oil inhibited contractions in guinea-pig ileum, rat duodenum and vas deferens, and rabbit jejunum and aorta in vitro (*27*, *28*). The essential oil also exhibited smooth muscle relaxant activity in guinea-pig tracheal muscle ($ED_{50}$ 22 µg/ml) and in an electrically stimulated ileum myenteric plexus/longitudinal muscle preparation ($ED_{50}$ 7.8 µg/ml) (*29*).

#### Behavioural effects

Inhalation of the essential oil had a weak tranquillizing effect in mice (*30*).

### *Clinical pharmacology*

An open multicentre study of 115 patients with herpes simplex infections of the skin and transitional mucosa demonstrated that external applications of a 1% lyophilized aqueous extract of Folium Melissae in a cream base reduced

the healing time of herpetic lesions from 10–14 days to 6–8 days (*18*). Treatment with the cream also prolonged the recidivation-free intervals, as compared with other topical virustatic preparations containing idoxuridine and tromantidine hydrochloride (*16*, *18*). A subsequent randomized, double-blind, placebo-controlled study of 116 patients with herpes simplex infections of the skin and transitional mucosa demonstrated a significant reduction in the size of herpetic lesions within 5 days in patients treated with the same cream ($P = 0.01$), as compared with placebo treatment (*17*, *18*).

## Contraindications

External use: none. Internal use: see Precautions.

## Warnings

No information available.

## Precautions

### *Carcinogenesis, mutagenesis, impairment of fertility*

A tincture of Folium Melissae was not mutagenic in vitro (*31*) and alcohol extracts had antimutagenic activity in vitro (*32*).

### *Pregnancy: teratogenic effects*

Internal use: no information available. Therefore, Folium Melissae should not be administered internally during pregnancy without medical supervision.

### *Pregnancy: non-teratogenic effects*

Internal use: no information available. Therefore, Folium Melissae should not be administered internally during pregnancy without medical supervision.

### *Nursing mothers*

Internal use: no information available. Therefore, Folium Melissae should not be administered internally during lactation without medical supervision.

### *Paediatric use*

Internal use: no information available. Therefore, Folium Melissae should not be administered internally to children without medical supervision.

### *Other precautions*

No information available on general precautions or precautions concerning drug interactions; or drug and laboratory test interactions; pregnancy.

## Adverse reactions

No information available.

## Dosage forms

Comminuted crude drug; powder, tea bags, dried and fluidextracts for infusions and other galenical preparations (*7*, *14*, *15*). Store in a tightly closed container, protected from light (*1*). Do not store in plastic containers (*7*).

## Posology

(Unless otherwise indicated)
Daily dosage for oral administration (for gastrointestinal disorders and as a sedative for nervous disturbances of sleep).

Infusion: 1.5–4.5 g crude drug per cup several times daily as needed (*15*); 45% alcohol extract (1 : 1): 2–4 ml three times daily (*5*); tincture (1 : 5 in 45% alcohol): 2–6 ml three times daily (*14*).

Daily dosage for topical application (for herpes labialis).

Cream containing 1% of a lyophilized aqueous extract applied 2–4 times daily from the appearance of prodromal signs to a few days after the healing of the lesions, for a maximum of 14 days (*14*, *18*).

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# Aetheroleum Menthae Piperitae

## Definition

Aetheroleum Menthae Piperitae is the essential oil obtained by steam distillation of the fresh overground parts of *Mentha* × *piperita* L. (Lamiaceae) (*1–4*).

## Synonyms

*Mentha piperita* (L.) Huds., *M. piperita* Stokes, *M. balsamea* Willd. (*5, 6*).

## Selected vernacular names

Amentha, american mint, balm mint, brandy mint, cabra-caa, curled mint, doun menta piperita, hierbabuena, hortela pimenta, Katzenkraut, lamb mint, la menta, lamint, menta piemonte, mentea peperina, mentha pepe, menthe, menthe anglaise, menthe poivrée, moto yuyo, nána, ni naa, ni'na el fulfully, pepermin, pepper mint, peppermint, Pfefferminze, Pfefferminzblätter, piperita, pudeena, pum hub, yerba mota (*5–7*).

## Geographical distribution

Commercially cultivated in eastern and northern Europe and the United States of America, and is found in Africa (*1, 5, 8, 9*).

## Description

A perennial herb, 30–90 cm high. Stems square erect or ascending, branched, the upper portion always quadrangular. Leaves opposite, petiolate, ovate-oblong to oblong-lanceolate, serrate, pointed; dark green on the upper surface. Flowers purplish, occur in thick, terminal, spicoid racemes of verticillasters; each flower shows a tubular calyx with 5 sharp, hairy teeth, a purplish, irregular, 4-cleft corolla, 4 short stamens, a 4-celled ovary and a projecting style ending in a bifid stigma. Fruit consists of 4 ellipsoidal nutlets (*5, 8, 10*).

## Plant material of interest: essential oil

### *General appearance*

A colourless, pale yellow or pale greenish-yellow liquid (*1, 2*).

### *Organoleptic properties*
Odour: characteristic, penetrating; taste: characteristic, pungent, followed by a sensation of cold (*1, 2*).

### *Microscopic characteristics*
Not applicable.

### *Powdered plant material*
Not applicable.

## General identity tests
Thin-layer and gas chromatography for characteristic monoterpene profiles (*1, 2*).

## Purity tests
### *Microbiological*
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*11*).

### *Chemical*
Acid value: not more than 1.4 (*1, 2*).
Relative density: 0.900–0.916 (*1–3*).
Refractive index: 1.457–1.467 (*1–3*).
Optical rotation: −10° to −30° (*1–3*).
Solvent solubility: miscible with ethanol (96%), ether and methylene chloride (*1, 2*).

### *Pesticide residues*
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*2*). For other pesticides, see the *European pharmacopoeia* (*2*), and the WHO guidelines on quality control methods for medicinal plants (*11*) and pesticide residues (*12*).

### *Heavy metals*
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*11*).

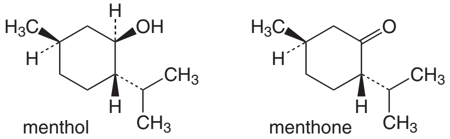
### *Radioactive residues*
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*11*) for the analysis of radioactive isotopes.

## Chemical assays

The monoterpene content determined by gas chromatography should be 1,8-cineole (6–14%), limonene (1–5%), menthone (14–32%), menthofuran (1–9%), isomenthone (2–10%), menthyl acetate (3–5%), menthol (30–55%), pulegone (not more than 4.0%) and carvone (not more than 1.0%). The ratio of 1,8-cineole to limonene should be greater than 2.0 (*1, 2*).

## Major chemical constituents

The major constituents are menthol (30–55%) and menthone (14–32%). Menthol occurs mostly in the free alcohol form, with small quantities as the acetate (3–5%) and valerate esters. Other monoterpenes present include isomenthone (2–10%), 1,8-cineole (6–14%), α-pinene (1.0–1.5%), β-pinene (1–2%), limonene (1–5%), neomenthol (2.5–3.5%) and menthofuran (1–9%) (*2, 6, 9, 13, 14*). The structures of the major monoterpenes, menthol and menthone, are presented below.




## Medicinal uses

### *Uses supported by clinical data*

Internally for symptomatic treatment of irritable bowel syndrome (*15–20*), and digestive disorders such as flatulence and gastritis (*21–23*). Externally for treatment of myalgia and headache (*21, 24–27*).

### *Uses described in pharmacopoeias and in traditional systems of medicine*

Internally and externally for the symptomatic treatment of catarrh and coughs (*21, 22*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of dysentery, diabetes, dysmenorrhoea, fevers, jaundice and urinary infections (*7*).

## Pharmacology

### *Experimental pharmacology*

#### Antimicrobial activity

Aetheroleum Menthae Piperitae inhibited the growth in vitro of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Enterococcus faecalis* and *Escherichia*

*coli* (*28–30*), but did not affect the growth of *Bacillus cereus*, *Penicillium cyclopium* or *Aspergillus aegyptiacus* (*28, 30*). The essential oil inhibited the growth in vitro of *Trichophyton equinum* and *T. rubrum* (at a concentration of 0.4 μg/ml) (*31*), *Aspergillus flavus*, *A. fumigatus* and *A. niger* (*32*).

### Antispasmodic activity

The essential oil had smooth muscle relaxant activity in guinea-pig ileum ($ED_{50}$ 26.0 mg/l) and trachea ($ED_{50}$ 87.0 mg/l) in vitro (*33*), and inhibited electrically induced contractions of guinea-pig ileum ($IC_{50}$ 0.176 mg/ml) in vitro (*34*). The essential oil decreased both the number and amplitude of spontaneous contractions, and inhibited spasms induced by barium chloride, pilocarpine and physostigmine in isolated segments of rabbit and cat ileum (inhibitory concentrations 0.05 μg/ml) (*35*). The essential oil (0.5 μmol/l) inhibited smooth muscle contractions of guinea-pig ileum in vitro induced by barium chloride, carbachol, histamine and potassium chloride (*36*). Both the essential oil and menthol act as calcium antagonists, since they inhibited the influx of calcium ions through smooth muscle of guinea-pig ileum and taenia coli isolated from humans (*36–39*). The essential oil and menthol inhibited smooth muscle contractions of guinea-pig ileum induced by potassium chloride ($IC_{50}$ 28.1 and 21 μg/ml, respectively) and induced electrically (11.5 and 7.7 μg/ml, respectively) (*40*). Both also inhibited $^{45}Ca^{2+}$ uptake induced by potassium ion-dependent depolarization in brain synaptosomes and retinal neurons, and inhibited specific binding of [$^{3}$H]nitrendipine to ileal smooth muscle, synaptosomes and retinal neurons (*40*). The essential oil relaxed carbachol-contracted guinea-pig taenia coli ($IC_{50}$ 22.1 μg/ml), and inhibited spontaneous contractions in isolated guinea-pig colon ($IC_{50}$ 25.9 μg/ml) and rabbit jejunum ($IC_{50}$ 15.2 μg/ml) (*41*). The essential oil also attenuated contractile responses in guinea-pig taenia coli induced by acetylcholine, histamine, serotonin (5-hydroxytryptamine) and substance P (*41*). Contraction of Oddi's sphincter induced by morphine was reversed after intravenous administration of the essential oil to guinea-pigs (1.0 mg/kg body weight). However, intravenous injection of the essential oil to guinea-pigs (25 mg/kg body weight) was found to increase spasms of the sphincter (*42*). Intragastric administration of the essential oil exhibited cholagogic activity in rats. This activity was attributed to (–)-menthol, a major constituent of the essential oil (*43*).

### Antifoaming activity

The essential oil (0.1%) had antifoaming and carminative activity in vitro; however, the antifoaming effect was less than that observed with a combination of dimethicone and silica (*44*).

### Toxicology

Intragastric administration of the essential oil (100 mg/kg body weight) to rats daily for 28 days induced histopathological changes (scattered cyst-like spaces)

in the white matter of the cerebellum. No behavioural or clinical symptoms due to the encephalopathy were observed (*45*).

## Clinical pharmacology

### Antispasmodic activity

#### Irritable bowel syndrome

Aetheroleum Menthae Piperitae is a carminative with antispasmodic activity that reduces intracolonic pressure (*22*). In an open study of 20 patients, an aqueous suspension of peppermint oil (British Pharmacopoeia Standard) injected along the biopsy channel of a colonoscope relieved colonic spasms within 30 seconds, allowing easier passage of the instrument or facilitating polypectomy (*16*). The essential oil relaxed the oesophageal sphincter when administered orally (15 drops [about 0.88 ml] oil in 30 ml water), decreasing the pressure differential between the stomach and oesophagus, and allowing reflux to occur (*46*).

In a double-blind, placebo-controlled, crossover clinical trial, 18 patients with symptoms of irritable bowel syndrome were treated daily with three enteric-coated gelatin capsules, each containing either 0.2 ml essential oil or a placebo for 3 weeks. Patients reported feeling significantly better while taking capsules containing the essential oil than when taking those containing placebo ($P < 0.01$) and considered the essential oil significantly better than the placebo in relieving abdominal symptoms ($P < 0.005$) (*19*). These results were confirmed in a later study (*15*). A matched-pair, placebo-controlled trial assessed the efficacy of the essential oil in the treatment of 40 patients with symptoms of irritable bowel syndrome. After 14 days of treatment with 1–2 enteric-coated gelatin capsules containing either 0.2 ml essential oil or a placebo three times daily, patients treated with the essential oil showed an increase in intestinal transit time, and subjective improvement in the feeling of fullness, bloating, bowel noises and abdominal pain, as compared with patients who received the placebo (*20*).

Administration of the essential oil to patients undergoing barium enemas relieved the associated colonic spasms (*47, 48*). However, two earlier trials failed to confirm the antispasmodic and analgesic activity of the essential oil in the treatment of irritable bowel syndrome (*49, 50*). A double-blind, placebo-controlled trial assessed the effects of peppermint oil in 34 patients with symptoms of irritable bowel syndrome. After 4 weeks of treatment with two capsules containing either 0.2 ml essential oil or a placebo three times daily, patients treated with the essential oil showed no significant difference in their overall symptoms, as compared with those who received the placebo treatment (*49*).

A prospective, randomized double-blind, placebo-controlled trial assessed the efficacy and safety of enteric-coated capsules containing 0.2 ml essential oil (one capsule 3–4 times daily for 1 month) for the symptomatic treatment of 110 patients with irritable bowel syndrome. After treatment, 79% of patients

in the treatment group and 43% of those in the placebo group experienced alleviation of severe abdominal pain; 83% of the treated group and 32% of the placebo group had reduced abdominal distention and a reduced stool frequency; 73% of the treated group and 31% of the placebo group had fewer bowel noises; and 79% of the treated group and 22% of the placebo group had less flatulence (*17*).

A review of five randomized, double-blind, placebo-controlled clinical trials assessed the efficacy of the essential oil in the symptomatic treatment of irritable bowel syndrome (*18*). By measuring the improvement of symptoms, the meta-analysis showed that two of the trials (*49*, *51*) did not show a significant difference between the essential oil and the placebo. However, three of the trials demonstrated significant improvements in symptoms after treatment with the essential oil (*15*, *19*, *52*). Although there were methodological flaws in most of the trials analysed, the analysis suggested that there was a significant positive effect of the essential oil ($P < 0.001$) on the symptomatic treatment of irritable bowel syndrome, as compared with the placebo (*18*).

### *Dyspepsia*

A double-blind, placebo-controlled multicentre study involving 45 patients with non-ulcer dyspepsia assessed the change in pain intensity and Clinical Global Impression Scale after treatment with an enteric-coated capsule containing a combination of the essential oil (90 mg) and caraway oil (50 mg). After 4 weeks of treatment with the essential oil/caraway oil capsules (one capsule three times daily), 63% of patients were free of pain; 89.5% had less pain; and 94.5% showed improvements in the Clinical Global Impression Scale (*23*). In another study, oral administration of the essential oil (0.2 ml) delayed the gastric emptying time in healthy volunteers and in patients with dyspepsia (*53*).

## Analgesic activity

A randomized, double-blind, placebo-controlled, crossover study assessed the efficacy of a combination product of the essential oil (peppermint oil) and Aetheroleum Eucalypti (eucalyptus oil) for headache relief in 32 patients. Five different preparations were used (all in 90% ethanol, to a final weight of 100 g): 10 g peppermint oil and 5 g eucalyptus oil; 10 g peppermint oil and traces of eucalyptus oil; traces of peppermint oil and 5 g eucalyptus oil; and traces of both peppermint oil and eucalyptus oil; or a placebo. The test preparations or placebo were applied topically to large areas of the forehead and temples, and the effects on neurophysiological, psychological and experimental algesimetric parameters were measured. The preparations improved cognitive performance, and induced muscle relaxation and mental relaxation, but had no effect on sensitivity to headache (*27*). A randomized, double-blind, placebo-controlled study assessed the efficacy of the essential oil in the treatment of 41 patients suffering from chronic tension headache. At each headache episode, patients were treated orally with two capsules of either paracetamol (1 g) or placebo, or exter-

nal application of 10% essential oil in ethanol, or a placebo solution. Compared with the placebo solution, the 10% essential oil preparation produced a significant ($P < 0.05$) reduction in headache intensity within 15 minutes. Paracetamol was also more effective than the oral placebo but did not differ significantly from topical treatment with the essential oil (*54*).

## Contraindications

Preparations of Aetheroleum Menthae Piperitae should not be used internally by patients with inflammation of the gastrointestinal tract or gall bladder, or with impaired liver function (*21*). Hypersensitivity to the essential oil has been reported (*55–57*).

## Warnings

Aetheroleum Menthae Piperitae preparations should not be applied to the face, especially the nose, of infants or young children (*21*, *22*). Keep out of reach of children.

## Precautions

### General

Patients with achlorhydria (due to medication with histamine $H_2$ receptor antagonists) should only use enteric-coated preparations (*19*, *58*).

### Carcinogenesis, mutagenesis, impairment of fertility

Aetheroleum Menthae Piperitae was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA1535 (*59*).

### Paediatric use

No information available. Therefore, Aetheroleum Menthae Piperitae should not be administered to children without medical supervision. (See also Contraindications and Warnings.)

### Other precautions

No information available on precautions concerning drug interactions; drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; or nursing mothers. Therefore, Aetheroleum Menthae Piperitae should not be administered during pregnancy or lactation without medical supervision.

## Adverse reactions

Following internal administration of Aetheroleum Menthae Piperitae, gastric complaints have been reported in individuals sensitive to the essential oil (*21*). The use of non-enteric-coated essential oil preparations has occasionally caused

heartburn, especially in patients suffering from reflux oesophagitis (*58*). Skin rashes, headache, heartburn, perianal burning, bradycardia, muscle tremors and ataxia have been reported as rare side-effects, usually associated with overdose (*18*, *56*, *60–65*). Recurrent muscle pain has been associated with the ingestion of the essential oil (*66*). Following external administration of Aetheroleum Menthae Piperitae, skin irritation has been reported (*58*).

## Dosage forms

Essential oil, concentrated peppermint emulsion, peppermint spirit and other galenic preparations (*1*, *21*). Store in a well-closed container, protected from light (*1*, *2*).

## Posology

(Unless otherwise indicated)

### Internal use

For digestive disorders, daily dosage: 0.2–0.4 ml essential oil three times daily in dilute preparations (*58*, *67*) or suspensions (*19*). By inhalation: 3–4 drops essential oil in hot water (*21*). Lozenges: 2–10 mg essential oil per lozenge (*58*).

For irritable bowel syndrome, daily dosage: 0.2–0.4 ml essential oil three times daily in enteric-coated capsules (*21*, *58*).

### External use

5–20% essential oil in dilute, semisolid or oily preparations; 5–10% essential oil in aqueous-ethanol; nasal ointments containing 1–5% crude drug (*21*).

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# Folium Menthae Piperitae

## Definition

Folium Menthae Piperitae consists of the dried leaves of *Mentha* × *piperita* L. (Lamiaceae) (*1–3*).

## Synonyms

*Mentha piperita* (L.) Huds., *M. piperita* Stokes, *M. balsamea* Willd. (*1, 4*).

## Selected vernacular names

Amentha, american mint, balm mint, brandy mint, cabra-caa, curled mint, doun menta piperita, hierbabuena, hortela pimenta, Katzenkraut, lamb mint, la menta, lamint, menta piemonte, mentea peperina, mentha pepe, menthe, menthe anglaise, menthe poivrée, moto yuyo, nána, ni naa, ni'na el fulfully, pepermin, pepper mint, peppermint, Pfefferminze, Pfefferminzblätter, piperita, pudeena, pum hub, yerba mota (*1, 4, 5*).

## Geographical distribution

Commercially cultivated in eastern and northern Europe and the United States of America, and is found in Africa (*1*, 3, *6*, *7*).

## Description

A perennial herb, 30–90 cm high. Stems square erect or ascending, branched, the upper portion always quadrangular. Leaves opposite, petiolate, ovate-oblong to oblong-lanceolate, serrate, pointed; dark green on the upper surface. Flowers purplish, occur in thick, terminal, spicoid racemes of verticillasters; each flower shows a tubular calyx with 5 sharp, hairy teeth, a purplish, irregular, 4-cleft corolla, 4 short stamens, a 4-celled ovary and a projecting style ending in a bifid stigma. Fruit consists of 4 ellipsoidal nutlets (*1, 7, 8*).

## Plant material of interest: dried leaves

### General appearance

Green to greenish-brown. Leaves whole, broken or cut; thin, fragile; whole leaf 3–9 cm long and 1–3 cm wide, often crumpled. Lamina oval or lanceolate; apex acuminate; margin sharply dentate; base asymmetrical. Venation pinnate,

prominent on the lower surface, with lateral veins leaving the midrib at an angle of about 45°. Lower surface slightly pubescent and secretory trichomes visible under a hand lens as bright yellowish points. Petiole grooved, usually up to 1 mm in diameter and up to 1 cm long (*2*).

### Organoleptic properties

Odour: characteristic, penetrating; taste: characteristic, aromatic (*2*).

### Microscopic characteristics

Upper epidermis composed of large, clear epidermal cells with sinuous, vertical walls and possessing few or no stomata, few glandular trichomes present; palisade parenchyma, comprising a layer of columnar cells rich in chloroplasts; spongy parenchyma, of 4–6 layers of irregularly shaped chloroplastid-containing cells and intercellular air-spaces. Lower epidermis of small epidermal cells with sinuous, vertical walls and numerous diacytic stomata; in the region of veins and midrib, exhibits non-glandular and glandular trichomes as outgrowths; non-glandular trichomes uniseriate, papillose, 1–8-celled; glandular trichomes have 1–2-celled stalk and 1–8-celled glandular head containing the essential oil. Calcium oxalate crystals absent; pollen grains spheroidal and smooth (*1*, *4*, *7*, *8*).

### Powdered plant material

Brownish-green. Fragments of leaf tissue with cells of epidermis having sinuous walls, cuticle striated over the veins, diacytic stomata present predominantly on the lower epidermis; epidermis fragments from near leaf margin with isodiametric cells showing distinct beading and pitting in anticlinal walls; covering trichomes short, conical, unicellular, bicellular or elongated, uniseriate multicellular (3–8 cells) with striated cuticle. Glandular trichomes of 2 types: either with unicellular base with small, rounded, unicellular head 15–25 µm in diameter; or with unicellular base with enlarged, oval multicellular head 55–70 µm in diameter composed of 8 radiating cells; dorsoventral mesophyll fragments with a single palisade layer and 4–6 layers of spongy parenchyma; yellowish crystals of menthol under the cuticle of secretory cells. Calcium oxalate crystals absent (*1*, *2*).

## General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography (*1*, *2*). Gas chromatography of the steam-distilled essential oil (*9*).

## Purity tests

### Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

### *Foreign organic matter*

Not more than 5% stems, the diameter of which must be not more than 1.5 mm; not more than 8% leaves showing brown stains due to *Puccinia menthae* (*2*); not more than 2% other foreign matter (*2*).

### *Total ash*

Not more than 15% according to the *European pharmacopoeia* (*2*); not more than 12% according to the *African pharmacopoeia* (*1*).

### *Acid-insoluble ash*

Not more than 1.5% (*2*).

### *Pesticide residues*

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*2*). For other pesticides, see the *European pharmacopoeia* (*2*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*11*).

### *Heavy metals*

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

### *Radioactive residues*

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

### *Other purity tests*

Sulfated ash, water-soluble extractive, alcohol-soluble extractive, and loss on drying tests to be established in accordance with national requirements.

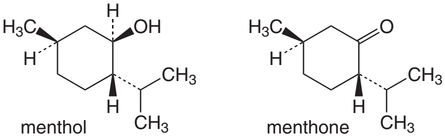
## Chemical assays

Whole and cut leaves contain not less than 1.2% and 0.9% (v/w) essential oil, respectively, determined as described in the *European pharmacopoeia* (*2*).

## Major chemical constituents

The major constituent of the leaves is the essential oil (0.5–4%), which contains menthol (30–55%) and menthone (14–32%). Menthol occurs mostly in the free alcohol form, with small quantities as the acetate (3–5%) and valerate esters. Other monoterpenes present include isomenthone (2–10%), 1,8-cineole (6–14%), α-pinene (1.0–1.5%), β-pinene (1–2%), limonene (1–5%), neomenthol (2.5–3.5%) and menthofuran (1–9%) (*2, 4, 6, 12, 13*).

The structures of the major monoterpenes, menthol and menthone, are presented below.




## Medicinal uses

### *Uses supported by clinical data*

None.

### *Uses described in pharmacopoeias and in traditional systems of medicine*

Symptomatic treatment of dyspepsia, flatulence and intestinal colic (*1*, *3*, *14*, *15*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

As an emmenagogue, vermifuge, lactation enhancer and sedative. Also used to treat bronchitis, bacillary dysentery, diabetes, diarrhoea, dysmenorrhoea, fevers, hypertension, jaundice, nausea, pain, and respiratory and urinary tract infections (*5*).

## Pharmacology

### *Experimental pharmacology*

#### Antimicrobial activity

Extracts of Folium Menthae Piperitae have antibacterial and antiviral activity in vitro. Addition of ground leaves to the agar medium inhibited the growth of *Salmonella typhimurium*, *Staphylococcus aureus* and *Vibrio parahaemolyticus* at concentrations of 0.1–2.0% (w/v) (*16*). Aqueous and ethanol extracts of the leaves reduced the number of plaques of the rinderpest virus at concentrations of 4–8 mg/ml (*17*). Aqueous extracts of the leaves demonstrated activity against the following viruses in egg and cell culture: Newcastle disease, herpes simplex, vaccinia, Semliki Forest and West Nile (*18*).

#### Smooth muscle contraction

A 31% ethanol extract of the leaves inhibited both acetylcholine- and histamine-induced smooth muscle contractions in guinea-pig ileum in vitro at a concentration of 10 ml/l (*19*, *20*). The results were similar to those obtained with 0.13 mg atropine (*19*). An aqueous flavonoid fraction isolated from a leaf

extract inhibited barium chloride-induced muscle contractions of guinea-pig ileum in vitro at a concentration corresponding to 0.5 g leaves/ml (*21*).

#### Choleretic activity

Injection of a leaf infusion (0.5 ml) or a flavonoid fraction (equivalent to 3.3 g leaves/kg body weight) increased the amount of bile acids in cannulated rats and dogs (dose 0.4 mg/kg body weight) (*21*, *22*). A mixture of flavonoids, isolated from the leaves, had choleretic activity in dogs (2 mg/kg body weight) (*23*). Flavomentin, a flavonoid isolated from the leaves, stimulated bile secretion and the synthesis of bile acids in dogs (2 mg/kg body weight) (*24*). Intragastric administration of a 30% ethanol extract of the leaves to rats (1 ml/kg body weight) increased bile flow by 43%. The extract did not induce sedation in mice at doses up to 10 ml/kg body weight (*20*).

#### Anti-oedema activity

Topical application of a methanol leaf extract to mice (2.0 mg/ear) inhibited ear oedema induced by 12-*O*-tetradecanoylphorbol-13-acetate (*25*).

#### Analgesic activity

Intragastric administration of a 30% ethanol extract of the leaves inhibited phenylbenzoquinone-induced writhing in mice ($ED_{50}$ 2.1 ml/kg body weight) (*20*).

#### Toxicology

Intragastric administration of a leaf extract (50 g leaves infused with 500 ml hot water for 10 minutes, then spray-dried) to 12 mice (4 g/kg body weight as a single dose) did not result in central nervous system depression, toxic effects or mortality (*26*).

### *Clinical pharmacology*

None.

## Contraindications

No information available.

## Warnings

No information available.

## Precautions

### *General*

Patients with gallstones should not use Folium Menthae Piperitae unless under medical supervision (*15*).

### Other precautions

No information available on precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Folium Menthae Piperitae should not be administered during pregnancy or lactation or to children without medical supervision.

## Adverse reactions

No information available.

## Dosage forms

Dried leaves (*2, 3*). Tincture and infusions (*6*). Store in a well-closed container, protected from light (*2*).

## Posology

(Unless otherwise indicated)

Daily dosage: 1–3 g crude drug three times daily (*14, 27*). Infusion: pour 150 ml hot water over 1.5–3.0 g (one tablespoon) dried leaves, steep for 10 minutes, strain and drink three times daily between meals (*6, 15, 28*). Tincture: 2–3 ml (1 : 5, 45% ethanol) three times daily (*14*).

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# Folium Ocimi Sancti

## Definition

Folium Ocimi Sancti consists of the fresh or dried leaves of *Ocimum sanctum* L. (Lamiaceae) (*1–3*).

## Synonyms

*Moschosma tenuiflorum* (L.) Heynhold, *Ocimum album* Blanco, *O. anisodorum* Muell., *O. brachiatum* Hasskarl, *O. flexuosum* Blanco, *O. frutescens* Burm., *O. gratissimum* Lour., *O. inodorum* Burm., *O. monachorum* L., *O. nelsonii* Zipp ex Span., *O. tenuiflorum* L., *O. virgatum* Blanco (*4*).

## Selected vernacular names

Badrooj, basilic des moines, bazsalikom levél, daun lampes, garden balsam, green tulsi, holy basil, huong nhu tịia, jagu lu myah, kamimebouki, kaphrao, kaprao, kemangi, kemangi laki, kra phrao, lampas, monk's basil, peihan, rayhhan, reihan, sacred basil, saling-kugon, saling-kugon ma, selaseh puteh, solasi, sulasi, sursa, tamole, thulasi, tjlsi, tulashi, tulasi, tulsi (*1, 4–9*).

## Geographical distribution

Indigenous to India and parts of north and eastern Africa, Hainan Island and Taiwan, China. It is cultivated in south-east Asia (*6, 8, 10*).

## Description

A herb or shrub, up to 1 m high, often much branched. Stem square, lower parts sub-serrate, higher parts slightly furrowed and more densely pubescent or sub-glabrous. Leaves simple, opposite, oblong, ovate or oval-oblong, 2.7–7.5 cm long, 1–3 cm wide, with acute top, cuneate, obtuse to rounded base, margin entire, undulate or serrate, both surfaces thinly pubescent and dotted; petiole 0.2–3.0 cm long. Calyx 0.2–0.4 cm long, with or without long or short hairs, ciliate, densely glandulose; upper lip 2.0–3.5 mm long, oval short-acuminate; lower lip 1.0–2.5 mm long, dentate, teeth linear-acuminate from an equal- or unequal-sided triangular to ovate base, 2 anterior teeth equalling or slightly surpassing the upper lip; fruiting calyx not completely closed by teeth. Upper part of the corolla villous and glandulose in the upper part; lobes of upper lip

rounded, lobes of lower lip obtuse to rounded. Nutlets obovoid, dark brown or black, 1–2 mm long; pericarp swells into a slimy mass when moistened (*6*, *8*, *11*, *12*).

## Plant material of interest: fresh or dried leaves

### *General appearance*

Leaves green to greenish-brown, 2.5–7.5 cm long, 1–3 cm wide, oblong, ovate or oval-oblong, with acute top, cuneate, obtuse to rounded base, pinnate veins, serrate or entire and undulate margin; thin but fleshy, both surfaces thinly pubescent; petiole cylindrical, 1–2 cm long, thinly pubescent (*1*).

### *Organoleptic properties*

Odour: characteristic, aromatic; taste: slightly pungent (*1*, *2*).

### *Microscopic characteristics*

Transverse section of the leaf through its midrib: upper epidermis consists of a layer of small, quadrangular transparent cells with thin walls and thin smooth cuticle. On tangential view, these cells are polygonal with straight or wavy walls. Lower epidermis consists of a layer of small, quadrangular transparent cells with thin walls and thin smooth cuticle. Trichomes bent, consisting of 2–6 cells; glandular trichomes short, Lamiaceae type, consisting of 1 stalk cell and 2–4 cells with rounded heads. Palisade parenchyma consists of layer of long cylindrical cells containing chlorophyll; spongy parenchyma consists of polygonal cells with thin, straight or slightly wavy side walls. Vascular bundles collateral type with collenchyma cells. Stomata diacytic, on upper and lower epidermis (*1*).

### *Powdered plant material*

Upper epidermis with diacytic stomata, glandular trichomes and palisade cells; lower epidermis with diacytic stomata and underlying spongy cells; 2- and 4-celled glandular trichomes; uniseriate, multicellular trichomes with collapsed cells; lignified fibres; spiral vessels; pollen grains rare; parenchyma and collenchyma from petioles (*2*).

## General identity tests

Macroscopic and microscopic examinations (*1*), and thin-layer chromatography (*2*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

### Total ash
Not more than 13% (*1*).

### Acid-insoluble ash
Not more than 1% (*1*).

### Sulfated ash
Not more than 20% (*2*).

### Water-soluble extractive
Not less than 5% (*1*).

### Alcohol-soluble extractive
Not less than 5.0% (*2*).

### Loss on drying
Not more than 14% (*2*).

### Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

### Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

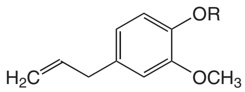
### Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

### Other purity tests
Chemical and foreign organic matter tests to be established in accordance with national requirements.

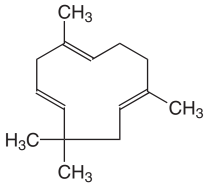
## Chemical assays
Contains not less than 0.5% essential oil (3). Gas chromatography and gas chromatography–mass spectroscopy methods are available for qualitative and quantitative determination of volatile constituents (*16*).

## Major chemical constituents

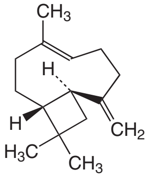
The main components are tannins (4.6%) and essential oil (up to 2%) (*1*). The amounts of the primary constituents of the essential oil vary according to the geographical distribution and variety of the source plant material: eugenol (up to 62%), methyleugenol (up to 86%), and α- and β-caryophyllene (up to 42%). Also present are methylchavicol, linalool and 1,8-cineole (*4*, *16–19*). The structures of the major constituents are presented below.




eugenol R = H
methyleugenol R = $CH_3$




α-caryophyllene




β-caryophyllene

## Medicinal uses

### *Uses supported by clinical data*

None. Although there are some preliminary clinical data supporting the use of Folium Ocimi Sancti for the treatment of diabetes, further trials are needed to substantiate the data.

### *Uses described in pharmacopoeias and in traditional systems of medicine*

Treatment of arthritis, asthma, bronchitis, common cold, diabetes, fever, influenza, peptic ulcer and rheumatism (*1*, *8*, *20*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of earache, epilepsy, heart disease, malaria, sinusitis, snake bites, stomach ache and vomiting. Also as an anthelminthic, to stimulate lactation, to prevent hair loss, and as a tonic (*7*).

## Pharmacology

### *Experimental pharmacology*

#### Analgesic activity

Intraperitoneal or intragastric administration of the fixed oil to mice (3 ml/kg body weight) significantly inhibited writhing induced by acetic acid ($P < 0.01$) (*21*). Intragastric administration of an aqueous suspension or a methanol extract of the leaves to mice (100 mg/kg body weight) showed analgesic activity in the hot-plate test (*22*).

### Antispasmodic activity

A 50% ethanol extract of the leaves inhibited histamine-induced bronchospasms and pre-convulsive dyspnoea in guinea-pigs when administered by gastric lavage (200 mg/kg body weight) (*23, 24*). Intragastric administration of the leaf essential oil or fixed oil to guinea-pigs (0.5 ml/kg body weight) inhibited bronchospasms induced by both histamine and acetylcholine, and pre-convulsive dyspnoea (*23–25*).

A hydroalcoholic extract of the leaves inhibited muscle spasms induced by histamine in guinea-pig ileum, and muscle spasms induced by acetylcholine, barium and histamine in guinea-pig small intestine in vitro (*26*). However, an aqueous extract showed no activity in either test system (*27*). In another study, aqueous extracts of the leaves inhibited muscle spasms induced by acetylcholine, histamine and carbachol in rabbit intestine in vitro (*28*).

### Antimicrobial activity

An ether or 95% ethanol extract of the leaves inhibited the growth in vitro of *Staphylococcus aureus* and *S. citreus* (*29, 30*) and of *Mycobacterium tuberculosis* (*29, 31*). A hot aqueous extract of the leaves inhibited the growth in vitro of *Trichophyton mentagrophytes* (*32*), and the growth of *Aspergillus fumigatus* and *A. niger* was inhibited in vitro when grown on agar plates containing the powdered leaves (*33*).

### Anti-inflammatory activity

Intragastric administration of a hydroalcoholic extract of the leaves or the essential oil to rats and guinea-pigs (10 ml/kg body weight) inhibited footpad oedema induced by histamine, serotonin and carrageenan (*23, 24*). Intragastric administration of the fixed oil and linolenic acid extracted from the leaf to rats inhibited footpad oedema induced by prostaglandin $E_2$, leukotriene, carrageenan and arachidonic acid (*34*). Intragastric administration of an aqueous leaf extract to rats (100 mg/kg body weight) inhibited footpad oedema induced by croton oil and carrageenan (*22*). Intraperitoneal administration of an aqueous leaf extract to rats (100 mg/kg body weight) also inhibited carrageenan-induced footpad oedema (*35*). A hydroalcoholic extract of the leaves inhibited the activity of prostaglandin synthetase by 88% in vitro at a concentration of 750 µg/ml (*36*). An aqueous leaf extract exhibited anticholinergic and antihistamine activity in guinea-pig ileum and small intestine in vitro (0.15 mg) (*27*).

### Antipyretic activity

Intragastric administration of a methanol leaf extract to rats (250 mg/kg body weight) suppressed fever induced by typhoid vaccine (*35*). However, intragastric administration of a hydroalcoholic extract of the leaves to rabbits (10 mg) did not suppress fever induced by yeast (*37*).

### Effect on sleeping time

Intraperitoneal administration of an aqueous or 70% ethanol extract (30–40 mg/kg body weight) of the leaves to mice potentiated sleeping time induced by hexobarbital and pentobarbital (*28, 38*).

### Immunostimulatory activity

Intragastric administration of an aqueous or methanol extract of the leaves to rats (100–500 mg/kg body weight) increased antibody titre in both sheep erythrocyte and Widal agglutination tests, thus demonstrating stimulation of the humoral immune response. The cellular immune response was also stimulated, as an increase in lymphocytosis and E-rosette formation was also seen (*39*). Intragastric administration of a leaf essential oil to rats (100 mg/kg body weight) enhanced the titres of both anti-sheep red blood cell and IgE antibodies (*40*).

### Endocrinological effects

The effects of a leaf extract on changes in serum triiodothyronine, thyroxine and cholesterol concentrations have been investigated in mice. After 15 days of treatment (0.5 g/kg body weight, by gastric lavage), significant decreases were observed in serum thyroxine concentration, hepatic lipid peroxidation and hepatic glucose-6-phosphate activities. No marked change in serum triiodothyronine levels was noted. The activities of superoxide dismutase and superoxide catalase were increased (*41*).

### Antiulcer activity

Intragastric administration of an ethanol extract of the leaves to rats reduced the concentration of plasma corticosterone, which had risen following 30 minutes of noise (100 dB), to normal levels (*42*). An organic solvent extract of the leaves had significant antioxidant activity in a variety of in vitro systems (*43*). Intragastric administration of a 70% ethanol extract of the leaves to rats (100 mg/kg body weight) prevented ulcers induced by acetylsalicylic acid and stress (*44*). Administration of the dried leaves to rats similarly prevented ulcers induced by cold and acetylsalicylic acid (*45*). However, intragastric administration of a methanol extract of dried leaves to mice (2 g/kg body weight) did not prevent stress-induced ulcers (*46*).

### Hypoglycaemic activity

Intragastric administration of a 50% ethanol extract of the leaves (250 mg/kg body weight) to albino rats with experimentally induced hyperglycaemia reduced blood glucose levels by 30% (*26, 47*). Intragastric administration of the leaves (50–400 mg/kg body weight) to rats with diabetes induced by streptozocin resulted in a reduction in blood glucose levels measured after fasting (*48*).

### Toxicity

Intragastric administration of eugenol (400–600 mg/kg body weight) has been reported to produce liver damage in mice, whose livers were experimentally depleted of glutathione (*49*). It was also cytotoxic in isolated rat hepatocytes (*50*). However, no generalized toxicity was reported in mice after a 50% ethanol extract of the leaves was injected either intraperitoneally (1 g/kg body weight) (*26*) or intradermally (10 g/kg body weight) (*51*).

## *Clinical pharmacology*

### Asthma

In a study without controls, oral administration of an aqueous extract of dried Folium Ocimi Sancti to 20 patients with asthma increased lung vital capacity and relieved laboured breathing (*52*).

### Glucose and cholesterol levels

A randomized, placebo-controlled, single-blind, crossover study assessed the effects of the dried leaves on the levels of blood glucose and serum cholesterol in 40 non-insulin-dependent diabetic patients. Patients received orally 2.5 g leaves daily for 4 weeks. Blood glucose levels, measured after fasting and eating, decreased by 17.6% and 7.3% respectively. Mean total cholesterol levels also decreased slightly (by 6.5%) during the treatment period (*20*). No adverse effects were observed.

# Contraindications

There are conflicting reports on the embryotoxicity of Folium Ocimi Sancti (*53*, *54*). The use of Folium Ocimi Sancti is therefore contraindicated during pregnancy and lactation.

# Warnings

No information available.

# Precautions

## *Drug interactions*

One study has shown that eugenol may be hepatotoxic in mice with glutathione-depleted livers (*49*). Therefore, Folium Ocimi Sancti should be used with caution in patients taking drugs such as paracetamol (acetaminophen) that deplete glutathione.

## *Carcinogenesis, mutagenesis, impairment of fertility*

A hot aqueous extract of fresh Folium Ocimi Sancti was not mutagenic in *Bacillus subtilis* H-17 (*rec*+) and M-45(*rec*–) at a concentration of 0.5 ml/disc (*55*).

Intragastric administration of the leaves prevented implantation of the embryo in various animal models (*54, 56*). Intragastric administration of the leaves (10% of feed) to male mice inhibited spermatogenesis (*57, 58*).

### *Pregnancy: teratogenic effects*

There are conflicting reports on the embryotoxicity of Folium Ocimi Sancti. In one study, a benzene leaf extract was neither teratogenic nor embryotoxic when administered intragastrically to rats (200 mg/kg body weight) (*53*). However, another study demonstrated that aqueous or benzene extracts of the leaves were embryotoxic when administered intragastrically to rats (100–200 mg/kg body weight) (*54*). (See also Contraindications.)

### *Pregnancy: non-teratogenic effects*

See Contraindications.

### *Nursing mothers*

See Contraindications.

### *Other precautions*

No information available on general precautions or precautions concerning drug and laboratory test interactions or paediatric use. Therefore, Folium Ocimi Sancti should not be administered to children without medical supervision.

## Adverse reactions

No adverse reactions have been reported in clinical trials (*20, 52*).

## Dosage forms

Crude drug and preparations thereof (*1*).

## Posology

(Unless otherwise indicated)
Daily dosage: 6–12 g crude drug as a decoction (*8*).

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# Oleum Oenotherae Biennis

## Definition

Oleum Oenotherae Biennis is the fixed oil obtained from the seeds of *Oenothera biennis* L. (Onagraceae).

## Synonyms

*Oenothera communis* Léveillé, *Oenothera graveolens* Gilib., *Onagra biennis* Scop., *Onagra vulgaris* Spach. (*1*).

## Selected vernacular names

Enotera, evening primrose, hhashyshat el hhimar, king's cureall, la belle de nuit, ligetszépeolaj, mematsuyoigusa, Nachtkerzenöl, onagre, raghan-e gole magrebi, teunisbloem (*1–7*).

## Geographical distribution

Indigenous to Europe and is naturalized in North America (*7*, *8*).

## Description

A biennial or occasionally an annual, up to 1.25 m high. Thick yellowish conical root produces compressed rosettes of obtuse basal leaves, from which arise much-branched reddish, rough stems; stems bear alternate, lanceolate to ovate, entire, 4 cm long, short petioled leaves. Flowers very fragrant, 3–5 cm in diameter, yellow, erect on spikes, 4-petalled; open in the evening and wilt after 1 night. Seed pods contain many small reddish-brown seeds. Plant hybridizes easily (*2*, *9*).

## Plant material of interest: fixed oil obtained from the seeds

### *General appearance*

A light-amber liquid.

### *Organoleptic properties*

Odourless; taste: oily.

## General identity tests

Standard methods for analysis of fatty acids (*1, 9*).

## Purity tests

### Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

### Chemical

Refractive index: 1.476–1.480 (*5*).
Specific gravity: 0.920–0.930 (*5*).

### Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

### Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

### Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

### Other purity tests

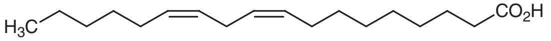
Foreign organic matter acid values to be established in accordance with national requirements.

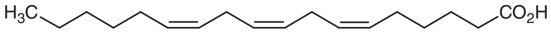
## Chemical assays

Concentration limits of linoleic acid (*cis*-linoleic acid) and γ-linolenic acid (*cis*-γ-linolenic acid) need to be established. However, based on literature data, values of not less than 60% and 7%, respectively, may be considered. A gas chromatography method is available for quantitative analysis (*13*).

## Major chemical constituents

The major constituents are linoleic acid (*cis*-linoleic acid) (65–80%), γ-linolenic acid (*cis*-γ-linolenic acid) (8–14%), oleic acid (6–11%), palmitic acid (7–10%) and stearic acid (1.5–3.5%). Other constituents include sterols and triterpene alcohols (*1, 3, 6, 14, 15*). The structures of linoleic acid and γ-linolenic acid are presented below.

linoleic acid 


γ-linolenic acid 


## Medicinal uses

### *Uses supported by clinical data*

Internally for symptomatic treatment of atopic eczema (*2, 16–21*), diabetic neuropathy (*22, 23*), and mastalgia (*24–26*). Clinical evidence for its use in the treatment of rheumatoid arthritis (*27–30*) is conflicting, as are the results of trials in women with premenstrual syndrome (*31–35*). Further well-designed clinical trials are needed to clarify these data. The results from clinical trials do not support the use of Oleum Oenotherae Biennis for the treatment of climacteric symptoms or psoriasis (*36, 37*).

### *Uses described in pharmacopoeias and in traditional systems of medicine*

Topical use for the treatment of minor bruises and wounds (*2*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

Taken internally for the treatment of asthma, coughs, gastrointestinal disorders, pain and whooping cough (*2, 9, 38*).

## Pharmacology

### *Experimental pharmacology*

#### Anti-allergic activity

Oleum Oenotherae Biennis was added to the diet (1 g/kg body weight, for 5 days) of guinea-pigs sensitized to ovalbumin prior to sequential allergen inhalation challenges. Treatment with the fixed oil reduced the severity of bronchial reactions following allergen challenge; the reactions were less severe in the animals challenged 80 minutes after treatment (86% reduction) than in those challenged after 10 minutes (33% reduction) (*39*).

#### Effects on cholesterol and triglyceride levels

Administration of the fixed oil to rabbits (15% of a high-cholesterol diet) for 6 weeks reduced total serum cholesterol and triglyceride levels, and increased high-density lipoprotein levels (*40*). A decrease in cholesterol and triglyceride levels in plasma and liver was observed in rats fed a diet containing the fixed oil (10% of a high-cholesterol diet) for 5 weeks (*41*). The fixed oil also increased the levels of high-density lipoprotein, IgG and leukocytes in the serum of mice fed a regular diet containing 10% fixed oil for 6 weeks (*42*). Levels of total serum

cholesterol and very-low-density lipoprotein were consistently lower in rats fed a high-cholesterol diet supplemented with 10% fixed oil for 13 weeks, after having been fed a regular diet for 8 weeks (since birth) (*43*).

### Inhibition of platelet aggregation

Administration of the fixed oil to rats (5 ml/kg body weight) inhibited adenosine diphosphate-induced platelet aggregation ex vivo (*14*). However, in another study no effect on adenosine diphosphate-induced platelet aggregation ex vivo was observed in rats fed a diet containing the fixed oil (10% of diet) (*41*). Administration of the fixed oil to rabbits (15% of a high-cholesterol diet) reduced platelet hyperaggregation ex vivo (*40*).

### Antihypertensive activity

Rats fed a diet containing 11% fixed oil for 7 weeks showed a decrease in the spontaneous development of hypertension (*41*, *44*). However, the vascular response to the vasoconstrictor hormones norepinephrine, angiotensin II or the calcium channel blocker verapamil remained unchanged (*44*). In another study, however, intragastric administration of the fixed oil to rats (1 ml daily for 3 months) significantly reduced the vascular response to renin and angiotensin II ($P < 0.05$), and significantly increased the formation of vascular prostacyclin-like activity ($P < 0.05$), compared with control rats which received olive oil (*14*). Intragastric administration of the fixed oil to rats enhanced the hypotensive effects of dihydralazine, clonidine and captopril (*45*).

Administration of the fixed oil (147 nmol/hour via an osmotic pump for 8 weeks) to male rats fed a fat-free diet attenuated the cardiovascular responses (increased heart rate and blood pressure) to chronic isolation stress (*46*). Administration of γ-linolenic acid (0.4 mg/kg body weight/hour, via an osmotic pump for 8 weeks) also attenuated the cardiovascular responses to chronic isolation stress in male rats genetically predisposed to hypertension (*47*). Administration of the fixed oil to rats (9% of diet) decreased cardiac arrhythmias induced by ischaemia (*48*).

### Antiulcer activity

Intragastric administration of the fixed oil to rats (10 ml/kg body weight) inhibited gastric mucosal damage resulting from ulcers induced by pylorus ligation, non-steroidal anti-inflammatory drugs, and hypothermic restraint. The same dose of the fixed oil also protected gastric mucosa from damage by necrotizing agents (0.6 mol/l hydrochloric acid, 0.2 mol/l sodium hydroxide and 80% ethanol) (*49*).

### Antiarthritic activity

Subcutaneous administration of the fixed oil to rats (4 mg/kg body weight) suppressed adjuvant-induced arthritis when administered 1–15 days after adjuvant injection (*50*). Intragastric administration of the fixed oil (0.2 ml/kg body

weight) stimulated phagocytosis, T-lymphocyte production and natural killer cell activity in cyclophosphamide-induced immune suppression in mice (*51*). Daily topical application of the fixed oil (10%) to the skin of pigs for 6 weeks enhanced cell proliferation (*52*).

### Nerve function

Administration of the fixed oil (10% of diet) to rats with streptozocin-induced diabetes corrected a decrease in nerve conduction velocity, but did not reduce the prolonged hypoxic time to conduction failure after 1 month of treatment. Capillary density of the endoneurium also increased. Treatment of the animals with flurbiprofen, a cyclooxygenase inhibitor, reduced the effect of the fixed oil (*53*). Intragastric administration of the fixed oil (1 g/kg body weight) for 6 weeks to rats with streptozocin-induced diabetes improved conduction velocity in the sciatic motor nerve and increased sciatic endoneural blood flow (*54*). In another study, administration of the fixed oil (5% of diet) to rats with streptozocin-induced diabetes prevented the decrease in nerve conduction velocity without affecting the levels of nerve sorbitol, fructose and myo-inositol, or the decrease in axonal transport of substance P (*55*).

### Anti-embryotoxic activity

Intragastric administration of the fixed oil (0.6 ml daily) to pregnant rats on days 4–8 of gestation significantly reduced the embryotoxic effects of ethanol (*56*).

## *Clinical pharmacology*

### Atopic eczema

A meta-analysis of nine placebo-controlled clinical trials (four parallel studies and five with crossover design) of Oleum Oenotherae Biennis in the symptomatic treatment of 311 patients with atopic eczema concluded that the fixed oil was more effective than placebo (*20*). However, two double-blind, placebo-controlled studies that were not included in the meta-analysis, one crossover trial of 123 patients (2–4 g for children, 6–8 g for adults, daily for 4 weeks) (*57*), and one parallel trial of 102 patients (dosage not stated) (*58*), reported negative results. In another double-blind, placebo-controlled study, the efficacy of the fixed oil in the treatment of 39 patients with chronic dermatitis of the hands was assessed. Patients received 6 g fixed oil or placebo daily for 16 weeks. Improvements were observed in both groups, but there was no significant difference between the two groups (*59*). A randomized double-blind, placebo-controlled crossover trial of 99 patients assessed the efficacy of oral administration of the fixed oil for symptomatic treatment of atopic eczema. Patients treated with 2–4 g fixed oil daily for 12 weeks showed a 30–45% improvement in the overall severity of the eczema, including a significant decrease in itching and scaling ($P < 0.002$), as compared with those that received the placebo (*21*). Similar results were reported in a multicentre study (*60*). In a double-blind,

parallel trial, oral administration of 430 mg oil daily to 37 patients with psoriasis resulted in no significant improvement in symptoms (*37*).

A double-blind, placebo-controlled study tested two doses of the fixed oil in the treatment of 51 children with atopic dermatitis. Patients were treated for 8 weeks with either a placebo, the fixed oil, or a combination of 50% placebo and 50% fixed oil (daily dose of 0.5 g/kg body weight, for all treatments). A significant improvement in the overall severity of the clinical symptoms was observed in patients treated with the fixed oil alone ($P$ = 0.046). This treatment also increased the concentration of omega-6 fatty acids in the erythrocyte cell membranes (*17*). In a study without controls, oral administration of the fixed oil (3 g) to 12 children daily for 4–20 weeks improved the symptoms of atopic eczema (*2*, *16*, *18*). In a double-blind, placebo-controlled, parallel trial, 58 children with atopic dermatitis were treated daily with either placebo or the fixed oil (2–4 g) for 16 weeks. Plasma concentrations of essential fatty acids increased in the group treated with the fixed oil. Symptomatic improvements occurred in both groups, but there was no significant difference between the two treatments (*61*). The major difficulty with this study was the use of a placebo containing sunflower oil, which has a similar spectrum of essential fatty acids to the fixed oil.

### Pharmacokinetics

The serum concentration of eight fatty acids over time was measured after oral administration of the fixed oil to six healthy volunteers. Six capsules of the fixed oil (500 mg each) were administered in both the morning and evening. The fatty acid concentrations in the serum were determined after each administration of the fixed oil as their methyl esters by gas chromatography–mass spectrometry. After administration of the fixed oil, γ-linolenic acid showed an absorption–elimination pattern, and its area under the curve at 24 hours and maximum concentration ($C_{max}$) were significantly increased over baseline values. The half-life of γ-linolenic acid was shorter after the evening dose (2.7 hours) than after the morning treatment (4.4 hours). Serum levels of dihomo-γ-linolenic acid and arachidonic acid did not increase after administration of the fixed oil (*62*).

### Rheumatoid arthritis

Four clinical trials have assessed the efficacy of the fixed oil for the treatment of rheumatoid arthritis in small numbers of patients (*27–30*). Three of the trials were unable to establish a significant benefit of using the fixed oil (*27*, *28*).

A 12-week prospective trial involving 20 patients with rheumatoid arthritis assessed the effects of the fixed oil (4.8 ml, equivalent to 360 mg γ-linolenic acid, daily). Prior to the study, all patients discontinued their pharmacological treatments (at least 4 weeks before the start) and non-steroidal anti-inflammatory drugs (4 days before the start). In addition to the fixed oil, patients received vitamin E daily and a product containing zinc, ascorbic acid, niacin and pyridoxine. The symptoms of rheumatoid arthritis, such as joint tenderness, swollen joints, morning stiffness and pain, were assessed at the beginning of the

trial and at 2-week intervals during treatment. Although three patients reported improvements in symptoms during treatment, the study concluded that there was no significant impact on the symptoms of rheumatoid arthritis (*27*). Another 12-week prospective study involving 20 patients with rheumatoid arthritis assessed the efficacy of 20 ml fixed oil daily (equivalent to 750 mg γ-linolenic acid daily) (*28*). The placebo group received olive oil (20 ml daily). All patients discontinued anti-inflammatory medications 7–10 days prior to the study. Although the plasma concentrations of prostaglandin $E_2$ decreased in four of the patients treated with the fixed oil, no statistically significant changes in symptoms were observed in either group (*27*). The third study was a 6-month, prospective, double-blind, placebo-controlled clinical trial involving 40 patients with rheumatoid arthritis and upper gastrointestinal lesions associated with the use of non-steroidal anti-inflammatory drugs. Nineteen patients received 6 g fixed oil and 120 mg vitamin E daily, while 21 patients in the placebo group received olive oil (6 g daily). Although all patients continued to take non-steroidal anti-inflammatory drugs, three in each group reduced their dosage by one tablet per day. The results of this trial showed a significant reduction in morning stiffness in patients receiving the fixed oil after 3 months of therapy, which was also seen after 6 months of treatment. A significant reduction ($P = 0.04$) in pain and articular index was seen only in patients treated with olive oil (*29*).

A significant benefit of the fixed oil was seen in a double-blind, placebo-controlled study which assessed the efficacy of the fixed oil, alone or in combination with fish oil, for the treatment of rheumatoid arthritis in 34 patients taking non-steroidal anti-inflammatory drugs. Following 12 months of treatment, a significant subjective improvement was observed in patients receiving either the fixed oil (540 mg daily) or the fixed oil and fish oil (450 mg and 240 mg daily, respectively), as compared with the placebo group. In addition, these patients had markedly reduced their intake of non-steroidal anti-inflammatory drugs (*30*).

### Premenstrual syndrome

A review of four clinical studies (three with crossover design) reported improvements in the symptoms of premenstrual syndrome (PMS) following treatment with the fixed oil (*31–33*). One of these, a double-blind, placebo-controlled crossover study, assessed the efficacy of the fixed oil in women with PMS. After 8 weeks, improvements were seen in all the major clinical symptoms of PMS in both groups. Symptoms improved by 60% in patients treated with the fixed oil and by 40% in the placebo group. Irritability and depression were notably improved in the group treated with the fixed oil (*31*). In a study without controls, 196 women with PMS received two capsules of the fixed oil (500 mg each) twice daily during the luteal phase of the menstrual cycle. The women scored their symptoms during the cycle before treatment and for two cycles after treatment. During the two cycles after treatment, irritability decreased by 77%, depression by 74%, breast tenderness and pain by 76%, headache by 71% and ankle swelling by 63%. These improvements were highly significant ($P < 0.001$)

(*31*). Another study without controls assessed the efficacy of the fixed oil in 68 women with severe PMS, who had failed to respond to at least one other therapeutic regime. Patients were treated with a graduated dosage of the fixed oil, starting with two 500 mg capsules twice daily in the luteal phase only, going up to four capsules twice daily during the whole cycle if there was no response to treatment. Total remission of symptoms was seen in 61% of patients; 23% had partial remission. Of the 36 women who had also experienced breast pain as part of PMS, 26 had total relief from breast pain, five had partial relief and five showed no improvement (*33*).

More recent reviews (*63*, *64*) have assessed the clinical trials: seven placebo-controlled trials were identified, only five of which were randomized. Five of the seven trials (three of which were randomized) reported improvements in the symptoms of PMS. However, two of the best-performed studies, both randomized, double-blind, placebo-controlled crossover studies, failed to show any beneficial effects of the fixed oil (*34*, *35*). In one study, 27 women with PMS received 12 capsules of the fixed oil (500 mg each) or placebo daily. Treatment with the fixed oil did not reduce either the magnitude or the cyclicity of symptoms (*34*). The other study of 38 women with PMS found no difference between the fixed oil (6 g daily for six cycles) and placebo in alleviating symptoms (*35*).

In a study without controls of 19 women with PMS, patients were treated with four capsules of the fixed oil (500 mg each) twice daily for five cycles. A reduction in the scores of individual symptoms (irritability, swollen abdomen, breast discomfort, depression, anxiety, fatigue and general oedema) and total PMS scores was observed after one cycle, and improvements continued over all five cycles (*65*). The clinical and biochemical effects of the fixed oil were investigated in 30 women with severe, incapacitating PMS. The patients were treated with 3 g fixed oil or placebo daily, beginning on day 15 of the cycle until the next menstrual period. Treatment with the fixed oil alleviated PMS symptoms, as compared with treatment with the placebo. No changes were found in the plasma levels of 6-keto-prostaglandin $F_{1\alpha}$, follicle-stimulating hormone, luteinizing hormone, prolactin, progesterone, estradiol or testosterone (*66*).

### Mastalgia

The effect of the fixed oil on mastalgia, one of the symptoms of PMS, was assessed in a randomized, double-blind, placebo-controlled crossover study. Seventy-three women were treated with the fixed oil or placebo for 3 months. In patients with both cyclical and non-cyclical mastalgia, treatment with the fixed oil significantly reduced breast pain and tenderness ($P < 0.02$–$0.05$) (*25*). Another double-blind, placebo-controlled clinical trial assessed the efficacy of the fixed oil in 42 women with cyclic breast pain and tenderness. Patients were treated with eight capsules (500 mg each) daily for 12 weeks. The fixed oil was significantly more effective than placebo in reducing nodularity, breast tenderness and irritability, as well as promoting a feeling of well-being ($P < 0.05$) (*67*).

A review of the randomized trials and studies without controls involving 291 women with severe persistent mastalgia was performed. Patients were treated with either the fixed oil (six capsules of 500 mg), bromocriptine (5 mg) or danazol (200 mg) daily for 3–6 months. In patients with cyclical mastalgia, good responses were obtained in 45% of patients treated with the fixed oil, in 47% treated with bromocriptine and in 70% treated with danazol. The response rate in patients with non-cyclical mastalgia was 27%, 20% and 31%, respectively. Adverse reactions were reported in 2% of patients treated with the fixed oil, in 33% of patients treated with bromocriptine and in 22% of those treated with danazol (*26*). A review of 17 years of drug treatment at a mastalgia clinic described the efficacy of daily administration of danazol (200 mg), bromocriptine (5 mg) and the fixed oil (six capsules of 500 mg) in 414 patients (324 with cyclical and 90 with non-cyclical mastalgia). Treatment with danazol was most effective (in 79% of patients); the fixed oil and bromocriptine were effective in 58% and 54% of patients, respectively. However, the rates of adverse reactions were higher in patients treated with danazol and bromocriptine (30% and 35%, respectively) than in those treated with the fixed oil (4%) (*24*).

### Diabetic neuropathy

Dietary supplementation with the fixed oil was associated with a clinical, neurophysiological and quantitative sensory improvement in 22 male and female patients with diabetic polyneuropathy (*22*). After a preliminary trial in 22 patients with diabetes, positive effects were also reported in many neurological and neurophysiological parameters in a parallel double-blind study of 111 male and female patients with mild diabetic neuropathy (*23*).

Oral administration of the fixed oil to male patients with diabetes and healthy male volunteers (20 g, enriched with vitamin E) daily for 1 week enhanced erythropoiesis and changed the serum fatty acid profiles in both groups. Inhibition of platelet-activating factor 4 and plasma β-thromboglobulin was also observed in both groups (*68*).

### Menopausal flushing

The efficacy of the fixed oil was evaluated in a randomized, double-blind, placebo-controlled study of 35 women with hot flushes. The women were treated with either four capsules of the fixed oil (500 mg each, supplemented with 10 mg natural vitamin E) or placebo twice daily for 6 months. No significant improvement in menopausal flushing was observed in women treated with the oil, as compared with the placebo (*36*).

### Uraemic skin disorders

The effects of oral administration of the fixed oil on plasma fatty acid concentrations and the symptoms of uraemic skin disorders (dryness, pruritus and erythema) were evaluated in a double-blind study of haemodialysis patients.

Patients treated with the fixed oil (2 g daily) for 6 weeks showed a significant increase in plasma dihomo-γ-linolenic acid ($P < 0.05$) and a significant decrease in uraemic pruritus ($P < 0.05$) (*69*).

## Contraindications

No information available.

## Warnings

Oleum Oenotherae Biennis may precipitate symptoms of undiagnosed temporal lobe epilepsy, particularly in schizophrenic patients or patients taking epileptogenic drugs such as phenothiazines (*70–72*).

## Precautions

### General

Oleum Oenotherae Biennis should be used with caution in patients with a history of epilepsy, particularly those with schizophrenia, or those taking epileptogenic drugs such as phenothiazines (*19*, *70*).

### Drug interactions

Oleum Oenotherae Biennis inhibited platelet aggregation in animals (*14*, *40*) and inhibited platelet-activating factor in humans (*68*). Therefore, patients taking anticoagulant drugs in conjunction with the fixed oil should be closely monitored.

### Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Oleum Oenotherae Biennis should not be administered during pregnancy or lactation or to children without medical supervision.

## Adverse reactions

Headaches, nausea, loose stools and diarrhoea following treatment with Oleum Oenotherae Biennis have been reported (*2*). Administration of the fixed oil precipitated symptoms of undiagnosed temporal lobe epilepsy in schizophrenic patients taking epileptogenic drugs, in particular phenothiazines (*72*).

## Dosage forms

Fixed oil, neat or in capsule form (*1*, *13*). Store in a well-filled, airtight glass container, protected from heat and light.

## Posology

(Unless otherwise indicated)

Daily dosage: 320–480 mg fixed oil (calculated as γ-linolenic acid) in divided doses for atopic eczema, and 240–320 mg in divided doses for mastalgia (*19*).

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# Rhizoma Piperis Methystici

## Definition

Rhizoma Piperis Methystici consists of the dried rhizomes of *Piper methysticum* G. Forst. (Piperaceae) (*1–3*).

## Synonyms

*Macropiper latifolium* Miq., *M. methystiscum* (G. Forst.) Hook. et Arnott, *Piper inebrians* Soland (*3*).

## Selected vernacular names

Ava, ava root, awa, gea, gi, kao, kava, kavakava, kava-kava, kava-kava root, kavapipar, kawa, kawa kawa, kawa pepper, Kawapfeffer, malohu, maluk, maori kava, meruk, milik, racine de poivre enivrant, Rauschpfeffer, rhizoma de kava-kava, rhizoma di kava-kava, yagona, yaqona (*3–5*).

## Geographical distribution

Indigenous to and cultivated in the islands of Oceania, from Hawaii to Papua New Guinea, with the notable exception of New Caledonia, New Zealand and most of the Solomon Islands (*5*).

## Description

A perennial shrub up to 7 m high, robust and fairly succulent. Leaves cordate, pointed, smooth and green on both sides, up to 25 cm long. Root can reach 60 cm in length and 8 cm in diameter; may eventually become a heavy knotted mass, 8–25 cm wide. Petioles up to 6 cm long; flowers in irregular spadices with lateral root up to 3 m long (*5*).

## Plant material of interest: dried rhizome

### *General appearance*

Irregular, transverse and longitudinal pieces, varying considerably in size and shape: 3–20 cm long and 1–5 cm in diameter. Outer surface light yellowish or greyish-brown, longitudinally wrinkled, with large whitish circular root scars.

Fracture coarsely fibrous, inner surface yellow-white; bark thin; xylem distinctly radiate; pith large (*1, 2, 6, 7*).

### Organoleptic properties

Odour: slight, agreeable; taste: sweetish, pungent, sometimes slightly bitter, followed by slight numbness (*1, 2, 7*).

### Microscopic characteristics

Transverse section through the xylem shows small channels with vascular bundles; cross section through the xylem shows narrow vessels, which are located around the pith and alternate with large pith rays. Additional vessels across the pith; xylem has tracheid-like elements; phloem has fewer and thinner-walled cells. Secretory canals contain a fine, brown resinous mass. Unpeeled rhizome has a narrow cork-layer. Primary bark contains rays of collenchyma, tissues, numerous resin and storage cells around the phloem (*1–3*).

### Powdered plant material

Light yellow-brown. Contains large oval pith cells. Secretion canals containing yellow to red-brown masses of resin; elongated cells of the medullary rays porous and slightly lignified. Vessels lignified and reticulate; fibres slightly lignified, large lumen and occasionally branched oval ends. Xylem parenchyma, cells lignified and slightly elongated. Numerous simple or 2–3 compound starch grains, the individual grains being spheroidal or planoconvex, 10–30 μm and sometimes up to 45 μm in diameter, many showing radial or triangular central clefts. Calcium oxalate crystals absent (*1, 2, 7*).

## General identity tests

Macroscopic, microscopic and microchemical examinations (*1, 2, 7*), and thin-layer chromatography for the presence of characteristic unsaturated α-pyrones known as kava pyrones (*1, 2, 8*).

## Purity tests

### Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*9*).

### Foreign organic matter

Not more than 2% (*1, 2*).

### Total ash

Not more than 8% (*1, 2*).

### *Acid-insoluble ash*
Not more than 1.5% (*1*).

### *Water-soluble extractive*
Not less than 5% (*1*).

### *Loss on drying*
Not more than 12% (*2, 3*).

### *Pesticide residues*
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*10*). For other pesticides, see the *European pharmacopoeia* (*10*), and the WHO guidelines on quality control methods for medicinal plants (*9*) and pesticide residues (*11*).

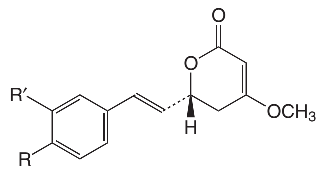
### *Heavy metals*
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*9*).

### *Radioactive residues*
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*9*) for the analysis of radioactive isotopes.

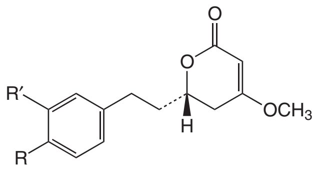
### *Other purity tests*
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

## Chemical assays
Contains not less than 3.5% kava pyrones, as determined by infrared absorption spectroscopy at $1705 \pm 5\,cm^{-1}$ (*2*). Complete qualitative analytical profiles can be obtained by high-performance liquid chromatography–electrospray mass spectrometry (*12*). A high-performance liquid chromatography method is also available for quantitative analysis (*3*).

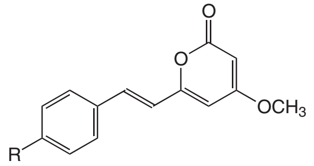
## Major chemical constituents
The major constituents are kava lactones (also known as kava pyrones) with the major lactones being kawain (1.8%), methysticin (1.2%), dihydromethysticin (0.5%), demethoxyyangonin (1.0%), yangonin (1.0%) and dihydrokawain (1.0%). At least 13 other lactones, two chalcones and a number of free aromatic acids are known (*3–5, 13*). The structures of the representative lactones are presented below.



kawain R = R′ = H
methysticin R, R′ = O-$CH_2$-O



dihydrokawain R = R′ = H
dihydromethysticin R, R′ = O-$CH_2$-O



yangonin R = $OCH_3$
demethoxyyangonin R = H

## Medicinal uses

### Uses supported by clinical data

Short-term symptomatic treatment of mild states of anxiety or insomnia, due to nervousness, stress or tension (*14–24*).

### Uses described in pharmacopoeias and in traditional systems of medicine

To induce relaxation, reduce weight and treat fungal infections (*5*).

### Uses described in folk medicine, not supported by experimental or clinical data

Treatment of asthma, common cold, cystitis, gonorrhoea, headaches, menstrual irregularities, urinary infections and warts (*4, 5*).

## Pharmacology

### Experimental pharmacology

#### Behavioural effects

Intraperitoneal administration of an aqueous extract of Rhizoma Piperis Methystici (62.5 mg/kg body weight) decreased the spontaneous activity of mice. This effect lasted for 2 hours without loss of muscle tone (*25*). The same extract, however, was not active in mice or rats when administered orally in single doses of 0.5–2.5 g/kg body weight. A dichloromethane extract of the rhizome (150 mg/kg body weight, administered intraperitoneally) decreased spontaneous motility by 46%, and markedly reduced motor control (by 50%)

in mice (*25, 26*). At this dose, the extract also induced hypnosis and analgesia (*25*). Intraperitoneal administration of aqueous, dichloromethane and lyophilized aqueous extracts of the rhizome (62.5–250 mg/kg body weight) reduced spontaneous activity in mice and rats (*27, 28*). Intraperitoneal administration of an aqueous or dichloromethane extract of the rhizome (120 mg/kg body weight) suppressed apomorphine-induced hyperactivity in rats (*25*). Intraperitoneal administration of a lipid-soluble fraction of an aqueous rhizome extract (doses up to 300 mg/kg body weight) decreased the conditioned avoidance response in rats. An aqueous extract, however, was inactive at doses up to 500 mg/kg body weight (*27*). Intraperitoneal administration of an extract of the rhizome (equivalent to 50–100 mg kava pyrones/kg body weight) or (±)-kawain, a synthetic kava lactone (10–50 mg/kg body weight), reduced muscle tone in cats (*29*).

**Analgesic activity**

Intraperitoneal administration of a dichloromethane extract of the rhizome (150 mg/kg body weight) produced analgesia in mice (*25*). Intraperitoneal or intragastric administration of an aqueous or lipid extract of the rhizome (150–250 mg/kg body weight) produced analgesia in mice, as measured by tail-flick reaction times and suppression of acetic acid-induced writhing (*30*). Both dihydrokawain and dihydromethysticin exhibited analgesic effects when administered intraperitoneally to rats (140 mg/kg body weight), as determined by an increase in tail-flick reaction times (*31*).

**Neurological effects**

Depression of the central nervous system was observed in rodents after intraperitoneal administration of an aqueous rhizome extract (50–170 mg/kg body weight) (*32*). Intraperitoneal administration of an aqueous extract (300 mg/kg body weight) or a chloroform extract (140 mg/kg body weight) of the rhizome depressed the central nervous system and potentiated the effects of barbiturates in mice. Administration of dihydromethysticin to mice potentiated pentobarbital-induced sleeping time by 400%, while dihydrokawain, yangonin and kawain were only moderately active (150–235%) (*33*). A dichloromethane extract of the rhizome administered intraperitoneally to mice (150 mg/kg body weight) induced hypnosis (*25*). The hypnotic and sedative effects of a dichloromethane rhizome extract (300 mg/kg body weight, administered intraperitoneally) were significantly prolonged in mice by the concurrent administration of ethanol (2 g/kg body weight; $P < 0.001$) (*30*). A saline extract of the rhizome had an effect on crayfish abdominal ganglia in vitro (0.05 g/ml) (*34*). Intraperitoneal administration of an extract of the rhizome (equivalent to 50–100 mg kava pyrones/kg body weight) to cats had a significant effect on EEG recordings, inducing high-amplitude delta waves, spindle-like formation, and continuous alpha- or beta-synchronization in amygdala recordings ($P < 0.001$). Hippocampal responses, following stimulation of the

amygdala nucleus, increased significantly in amplitude in cats treated intraperitoneally with the rhizome extract (equivalent to 100 mg kava pyrones/kg body weight; $P < 0.01$) or (±)-kawain (50 mg/kg body weight; $P < 0.05$) (*29*).

The neuroprotective effects of an acetone extract of the rhizome and kava pyrones have been demonstrated both in vivo and in vitro. A standardized acetone extract of the rhizome, methysticin and dihydromethysticin protected rodents against hypoxia or ischaemia-induced cerebral damage (*35*). The standardized extract also protected against neuronal damage in cultured neurons from chick embryo cerebral hemispheres (*36*).

Although the neuroprotective mechanisms of the rhizome are not well understood, recent investigations have indicated that kava pyrones may exert their effects by activating several neurotransmitter systems, such as the adrenergic (*37*), mesolimbic dopaminergic (*38*), gabaminergic (*39*), glutamatergic (*40, 41*), and serotonergic receptor systems (*42, 43*). An extract of the rhizome containing 58% kava pyrones enhanced the binding of [$^3$H]muscimol to γ-aminobutyric acid-A receptors in a concentration-dependent manner in rat hippocampus, amygdala and medulla oblongata in vitro ($ED_{50}$ 200–300 μmol/l) (*39*). However, another study found no significant interaction in vitro or in vivo of a dichloromethane rhizome extract or kava pyrones with γ-aminobutyric acid (A and B) or benzodiazepine receptor binding sites (*44*). Both kawain and dihydromethysticin (10–100 μmol/l) reduced the field potential changes induced by the serotonin-1A agonist, ipsapirone, in the CA1 and CA3 areas of guinea-pig hippocampal slices in vitro. These results suggest that both compounds may modulate serotonin-1A receptor activity (*43*). Methysticin and kawain inhibited the uptake of $^3$H-labelled norepinephrine, but not of $^3$H-labelled serotonin, in synaptosomes prepared from the cerebral cortex and hippocampus of rats (*37*). Intragastric administration of (+)-dihydromethysticin in a single dose (100 mg/kg body weight), or chronic intragastric administration of (±)-kawain (10.8 mg/kg body weight) daily for 78 days to rats did not alter dopamine or serotonin levels in the striatal or cortical brain regions (*45*).

## Anticonvulsant activity

Intraperitoneal administration of an aqueous extract (300 mg/kg body weight) or a chloroform extract (140 mg/kg body weight) of the rhizome to mice inhibited strychnine-induced convulsions (33). The anticonvulsant activity of methysticin and other kava pyrones against electroshock- and chemically-induced seizures has been demonstrated in mice and rats (*46–48*). Intraperitoneal administration of dihydromethysticin and dihydrokawain inhibited electroshock-induced seizures at doses of 25 and 60 mg/kg body weight, respectively, in mice and rats (*47*). Methysticin (10–100 μmol/l) was also active in different in vitro models of seizure-like events using extracellular recordings in rat temporal cortex slices containing the hippocampus and entorhinal cortex. Methysticin suppressed epileptiform activity independent of the stimulus (low calcium or magnesium, or high potassium perfusion medium), suggesting a

direct effect of the compound on neuron membranes, thus inhibiting neuron excitability (*40*). Other studies have demonstrated that (+)-kawain and (±)-kawain inhibited voltage-dependent calcium and sodium channels of rat cerebrocortical synaptosomes (*41, 49, 50*). In these synaptosomes, it was also shown that (±)-kawain inhibited the increase in intracellular calcium and glutamate release induced by veratridine and potassium chloride (*49*). Both (±)-kawain and methysticin inhibited voltage-dependent sodium channels in rat CA1 hippocampal neurons in vitro (1–400 μmol/l) (*51*).

### Antispasmodic activity

An aqueous rhizome extract, kawain, dihydrokawain, methysticin and dihydromethysticin inhibited serotonin and nicotine-induced contractions of guinea-pig ileum in vitro (*52, 53*). The antispasmodic effects were attributed to a direct musculotropic action. Dihydromethysticin also inhibited contractions of rat colon and uterus in vitro induced by serotonin, acetylcholine and barium (*53*). Desmethoxyyangonin, dihydromethysticin and kawain inhibited serotonin-induced contractions of rat uterus in vitro at concentrations of 3.2, 7.5 and 10.0 μg/ml, respectively (*54*). Aqueous, dichloromethane and lyophilized extracts of the rhizome induced relaxation of rat uterus in vitro ($ED_{50}$ 22.5 μg/ml) (*28*). The effects of an aqueous extract of the rhizome on muscle contractility and neuromuscular transmission were investigated in mouse hemidiaphragms and frog sartorius muscles in vitro using twitch tension and intracellular recording techniques. The extract (2–5 mg/ml) induced muscle relaxation by direct action on muscle contractility rather than by inhibition of neuromuscular transmission (*55*).

### Antimicrobial activity

A hydroalcoholic extract of the rhizome inhibited the growth in vitro of *Aspergillus fumigatus*, *A. niger*, *Penicillium digitatum*, *Rhizopus nigricans*, *Trichophyton mentagrophytes*, *Candida albicans* and *Saccharomyces pastorianus* (*56*). However, an aqueous extract of the rhizome did not inhibit the growth in vitro of *Trichophyton rubrum*, *Microsporum canis* or *Epidermophyton floccosum* (*57*).

## *Clinical pharmacology*

### Anxiety

At least seven double-blind, controlled clinical studies have assessed the efficacy of two extracts of Rhizoma Piperis Methystici for symptomatic treatment of anxiety (*17, 18, 21–24, 58*). Two of these studies were performed with a hydroalcoholic extract standardized to contain 15% kava pyrones (*22, 58*), while the other studies used an extract standardized to contain 70% kava pyrones (*17, 18, 21, 23, 24*).

Two placebo-controlled trials investigated the effect of both standardized extracts in women with climacteric psychosomatic disturbances. In the first study, 40 such women were treated with either a placebo or 200–400 mg extract

(30–60 mg kava pyrones) daily for 8–12 weeks. Using the Kuppermann Index and Anxiety Status Index, the extract was found to be superior to the placebo (*22*). In the second study, a further 40 such women were treated with 300 mg extract (210 mg kava pyrones) daily for 8 weeks in a randomized, placebo-controlled, double-blind study. The outcome was assessed using the Hamilton Anxiety Rating Scale; the Depression Status Inventory and the Kuppermann Index were also used. The total score on the Hamilton Anxiety Rating Scale decreased after 1 week of treatment with the extract, and reached a plateau at 4 weeks. The therapeutic response to the extract was significant, as compared with the response to the placebo ($P < 0.001$) (*23*). After 8 weeks of treatment with the extract, the mean score on the Hamilton Anxiety Rating Scale decreased from 31.1 to 5.5. In the group which received the placebo, the mean score decreased from 30.15 to 22.50. The mean score on the Depression Status Inventory decreased significantly from 42.5 to 24.8 ($P < 0.01$). The mean score on the Kuppermann Index also decreased significantly from 20.35 to 3.60 ($P < 0.01$) (*23*).

A double-blind, placebo-controlled study of 58 patients with symptoms of anxiety, tension or agitation of non-psychotic origin assessed the effectiveness of the extract containing 70% kava pyrones (equivalent to 210 mg kava pyrones) daily for 4 weeks. The outcome was assessed using the total score on the Hamilton Anxiety Rating Scale, and other rating scales (the Erlanger Scale for Anxiety, Clinical Global Impressions and the Fischer Somatic Symptoms). After 1 week, patients treated with the extract showed a reduction in the total score on the Hamilton Anxiety Rating Scale as compared with the placebo group. The difference between the scores of the two groups increased after 4 weeks of treatment (*17*).

A randomized double-blind comparative study assessed the efficacy of the extract containing 70% kava pyrones in 172 patients with symptoms of anxiety, tension and agitation of non-psychotic origin. Patients received either 300 mg extract (210 mg kava pyrones), 15 mg oxazepam or 9 mg bromazepam daily for 6 weeks. The main criterion for assessment was the total score on the Hamilton Anxiety Rating Scale. No significant difference was observed between the treatments (*24*). In another randomized study which involved several centres, the efficacy of the extract containing 70% kava pyrones was tested in 100 patients with anxiety of non-psychotic origin (as defined in the *Diagnostic and statistical manual of mental disorders*, 3rd ed. (*59*)). Patients were treated with either a placebo or 300 mg extract (equivalent to 210 mg kava pyrones) daily for 24 weeks and the outcome was assessed using the Hamilton Anxiety Rating Scale. Adjunct rating scales were the Clinical Global Impressions and Von Zerssen mood scale. In patients treated with the extract, the decrease in the Hamilton Anxiety Rating Scale (mean scores of 30.7 and 9.7 at weeks 0 and 24, respectively) was significant as compared with the placebo group ($P < 0.005$). The scores on the Clinical Global Impressions and Von Zerssen mood scale also improved after 24 weeks of treatment with the extract (*21*). A randomized study of 58 patients also assessed the efficacy of the extract containing 70% kava pyrones for the treatment of anxiety of non-psychotic origin. Patients were treated with either a

placebo or 300 mg extract (equivalent to 210 mg kava pyrones) daily for 4 weeks and therapeutic efficacy was assessed using the Hamilton Anxiety Rating Scale. After 1 week, there was a significant reduction in the scores (mean scores of 25.6 and 16.2 at weeks 0 and 1, respectively) in the treated group as compared with the placebo group ($P = 0.004$) (*18*).

A randomized, double-blind pilot study investigated the effects of the extract containing 15% kava pyrones in 59 patients with pre-operative anxiety (*58*). Although improvements in mood were observed using a psychostatus score, only two doses of the extract (equivalent to 60 mg kava pyrones daily) were administered, and thus the clinical significance of this study is questionable.

An additional nine double-blind studies have been performed with (±)-kawain (*60, 61*). Two of the studies were comparative studies and seven were placebo-controlled. Therapeutic anxiolytic activity was achieved with doses of 200–600 mg (±)-kawain daily (*60*). Kawain is available in Germany and Switzerland as an over-the-counter medication.

## Insomnia

Two single-blind and four double-blind, placebo-controlled clinical trials investigated the effect of a rhizome extract standardized to contain 70% kava pyrones on EEG recordings, and intellectual and motor functions of healthy volunteers (*14, 16, 62–65*). Changes in EEG recordings and psychomotor test results showed no evidence of a decrease in vigilance or responsiveness in volunteers treated with 600 mg extract (equivalent to 420 mg kava pyrones) daily for 5 days (*64, 65*). Examination of EEG recordings during sleep of healthy volunteers given a single dose of 300 mg extract (equivalent to 210 mg kava pyrones) showed an increased sleep spindle density of 20% and an increase in slow-wave sleep (i.e. deep sleep), but the rapid eye movement phase was not suppressed (*14*). Daily doses of 300 or 600 mg extract (equivalent to 210 or 420 mg kava pyrones), respectively, for 1 week increased the beta/alpha index typical for the pharmaco-EEG profile of anxiolytics. The increase in beta activity was most marked in the $beta_2$ range (*16*). In two studies, administration of 300 mg extract (equivalent to 210 mg kava pyrones) daily for either 8 or 14 days, taken with or without ethanol, had no influence on the safety-related performance of healthy volunteers (*62, 63*).

In a randomized, double-blind crossover study involving 12 healthy volunteers, administration of daily single doses of a rhizome extract standardized to contain 30% kava pyrones (400 mg extract containing 120 mg kava pyrones) was compared with daily single doses of diazepam (10 mg) or a placebo in a 7-day trial. Changes in EEG recordings and psychometric test results showed no evidence of a decrease in vigilance in the group treated with the extract (*66*). Safety-related performance was assessed in another study after administration of an extract standardized to contain 30% kava pyrones, bromazepam or a combination of extract and bromazepam. Safety-related performance remained unaffected in healthy volunteers treated daily with 400 mg extract (equivalent

to 120 mg kava pyrones for 14 days), whereas it was impaired after treatment with bromazepam (9 mg daily) or the extract/bromazepam combination. No differences were observed following treatment with bromazepam or the combination, indicating that the extract did not have an additive effect when given in combination with bromazepam (*67*).

## Contraindications

During pregnancy and lactation, and in patients with endogenous depression (*15*) or liver disease.[1]

## Warnings

Rhizoma Piperis Methystici should not be taken for more than 3 months without medical advice. Even when administered within the recommended dosage range, motor reflexes and the ability to drive or operate heavy machinery may be adversely affected (*15*).

## Precautions

### Drug interactions

The effectiveness of centrally acting drugs such as alcohol, barbiturates and other psychopharmacological agents may be potentiated (*15*). One case of possible drug interaction between Rhizoma Piperis Methystici, alprazolam, cimetidine and terazosin has been reported (*69*). The clinical significance of this interaction has not yet been established.

### Carcinogenesis, mutagenesis, impairment of fertility

Oral administration of up to 600 mg/kg body weight of a standardized extract containing 70% kava pyrones did not increase the formation of micronucleated polychromatic erythrocytes and did not lead to any change in the ratio of polychromatic to normochromatic erythrocytes. There was no increase in the number of revertants in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 with or without metabolic activation, at doses up to 2.5 mg/plate in the *Salmonella*/microsome assay (3).

### Pregnancy: teratogenic effects

See Contraindications.

### Pregnancy: non-teratogenic effects

See Contraindications.

[1] Several cases of liver toxicity have been reported in Europe following use of herbal products containing extracts of Rhizoma Piperis Methystici (*68*).

### Nursing mothers

See Contraindications.

### Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; or paediatric use. Therefore, Rhizoma Piperis Methystici should not be administered to children without medical supervision.

## Adverse reactions

In a surveillance study involving 4049 patients who received a standardized extract of Rhizoma Piperis Methystici containing 70% kava pyrones (150 mg extract, equivalent to 105 mg kava pyrones) orally daily for 7 weeks, adverse reactions were reported in 61 patients (1.5%). The major reactions were gastrointestinal complaints or allergic skin reactions (*3, 20*). In a study of 3029 patients given a standardized extract of the rhizome containing 30% kava pyrones (800 mg extract, equivalent to 240 mg kava pyrones) orally daily for 4 weeks, adverse reactions were reported in 2.3% of patients. Nine cases of allergic reactions, 31 cases of gastrointestinal complaints, 22 cases of headache or dizziness, and 11 cases of other undefined problems were reported (*3, 70*). Chronic administration of the rhizome or preparations thereof may cause a transient, yellow discoloration of the skin and nails, which is reversible upon discontinuation of the drug (*15*). Excessive, chronic abuse of infusions of the rhizome has been historically associated with a scaly, eruptive dermopathy of unknown etiology (*71*). Allergic skin reactions and ichthyosis have also been reported (*72–74*). In two patients, a reaction was seen in areas rich in sebaceous glands following 3 weeks of systemic antidepressant therapy with the rhizome. The reaction resulted in the formation of papules and plaques on the face, and ventral and dorsal thorax (*75*). One study in an Australian aboriginal community found that chronic abuse of the rhizome led to malnutrition and weight loss, increased levels of γ-glutamyltransferase, decreased levels of plasma protein, and reduced platelet volume and lymphocyte numbers (*76*). In a healthy volunteer, disturbances of visual accommodation, such as enlargement of the pupils, and disturbances in oculomotor equilibrium, were reported following the ingestion of large doses of kava (77). Chronic consumption (6 months) of large quantities of an infusion of the rhizome (5–6 cups daily) has been reported to cause anorexia, diarrhoea and visual disturbances (*73*). A single case report of athetosis involving the limbs, trunk, neck and facial musculature, with marked athetosis of the tongue, was associated with chronic consumption of large quantities of the rhizome (*78*).

There is one report of acute hepatitis in a 39-year-old woman following ingestion of a rhizome preparation (*79*). However, the identity of the material was not authenticated.

## Dosage forms

Comminuted crude drug and extracts for oral use (*15*). Store in a tightly closed container, away from light.

## Posology

(Unless otherwise indicated)
Daily dosage: crude drug and extracts equivalent to 60–210 mg kava pyrones (*15, 18, 21–24*).

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# Cortex Pruni Africanae

## Definition

Cortex Pruni Africanae consists of the dried bark of the trunk of *Prunus africana* (Hook. f.) Kalkman (Rosaceae).

## Synonyms

*Pygeum africanum* Hook. f. (*1*, *2*).

## Selected vernacular names

African plum tree, African prune, armaatet, bitter almond, Bitteramandel, chati, inkhokhokho, inyangazoma-elimnyama, kiburabura, lemalan migambo, mueri, muiru, murugutu, mutimailu, mweria, mwiritsa, nuwehout, ol-koijuk, oromoti, red stinkwood, rooistinhout, tenduet, tendwet, twendet, umdumizulu, umkakase, umkhakhazi, umlalume (*1*, *3–9*).

## Geographical distribution[1]

Found in mountain forests of equatorial Africa including Angola, Cameroon, Ethiopia, Ghana, Kenya, Madagascar, Malawi, Mozambique, Republic of Congo, South Africa, Uganda, United Republic of Tanzania, Zambia and Zimbabwe (*2*, *3*, *8*).

## Description

An evergreen tree, usually 10–25 m high, with straight, cylindrical trunk and dense, rounded crown. Leaves alternate, 8–12 cm long, long-stalked, simple, elliptic, bluntly pointed at apex, with shallow crenate margins; leathery, deep green and glossy, with midrib sharply impressed or channelled on upper surface and strongly prominent on underside; smell of almonds when bruised. Leafstalks and young branchlets often reddish. Flowers small, white or cream, fragrant, in axillary racemes 3–8 cm long; corolla lobes up to 2 mm long. Fruits cherry-shaped, red to purplish-brown, 8–12 mm in diameter; very bitter flesh and bony stone. Wood pale red, with strong cyanide smell when freshly cut,

[1] Owing to overexploitation and other factors, *Prunus africana* has been listed in Appendix II of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (*10*).

darkening to rich dark red or mahogany-brown on exposure to air; straight-grained and even textured, strong and elastic, very hard and very heavy (*3*, *8*, *11*).

## Plant material of interest: dried trunk bark

### *General appearance*

Red to blackish-brown, deeply square-fissured or corrugated (*1*, *3*, *8*).

### *Organoleptic properties*

Odour: strong, characteristic almond smell (*11*).

### *Microscopic characteristics*

To be established in accordance with national requirements.

### *Powdered plant material*

To be established in accordance with national requirements.

## General identity tests

Macroscopic examination (*3*, *8*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

### *Pesticide residues*

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

### *Heavy metals*

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

### Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

### Other purity tests

Chemical, foreign organic matter, total ash, acid-insoluble ash, sulfated ash, water-soluble extractive, alcohol-soluble extractive and loss on drying tests to be established in accordance with national requirements.

## Chemical assays

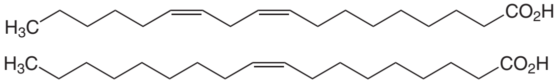
Qualitative and quantitative analysis for the major constituents, docosanol and β-sitosterol, are performed by gas chromatography–mass spectrometry (*15, 16*). Quantitative analysis of docosyl (*E*)-ferulate is performed by high-performance liquid chromatography (*17*).

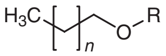
## Major chemical constituents

The purported active constituents of a lipophilic extract of Cortex Pruni Africanae include docosanol (0.6%) and β-sitosterol (15.7%). Other major constituents include alkanols (tetracosanol [0.5%] and *trans*-ferulic acid esters of docosanol and tetracosanol), fatty acids (62.3%, comprising myristic, palmitic, linoleic, oleic, stearic, arachidic, behenic and lignoceric acids); sterols (sitosterone [2.0%] and daucosterol) and triterpenes (ursolic acid [2.9%], friedelin [1.4%], 2-α-hydroxyursolic acid [0.5%], epimaslinic acid [0.8%] and maslinic acid) (*2, 15–21*). The structures of docosanol, tetracosanol, linoleic acid, oleic acid, β-sitosterol, sitosterone, ursolic acid and friedelin are presented below.

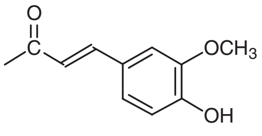
linoleic acid

oleic acid

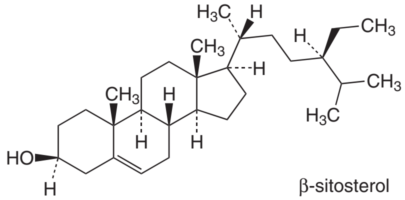


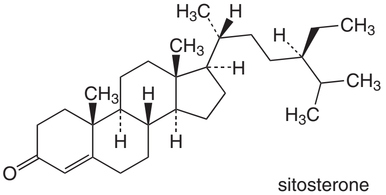

| | *n* | R |
|---|---|---|
| docosanol | 20 | H |
| tetracosanol | 22 | H |
| docosyl (*E*)-ferulate | 20 | (*E*)-ferulyl |
| tetracosyl (*E*)-ferulate | 22 | (*E*)-ferulyl |



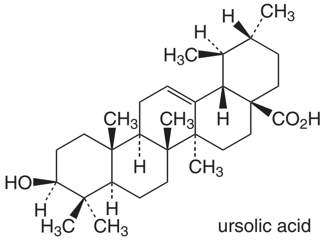

(*E*)- ferulyl



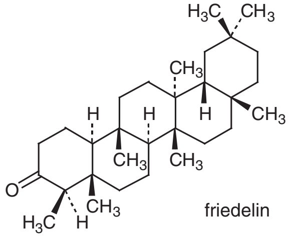
β-sitosterol



sitosterone



ursolic acid



friedelin

# Medicinal uses

## *Uses supported by clinical data*

Treatment of lower urinary tract symptoms of benign prostatic hyperplasia (BPH) stages I and II, as defined by Alken (e.g. nocturia, polyuria and urinary retention), in cases where diagnosis of prostate cancer is negative (*22–34*).

## *Uses described in pharmacopoeias and traditional systems of medicine*

None.

## *Uses described in folk medicine, not supported by experimental or clinical data*

As a purgative, for the treatment of stomach and intercostal pain (*3, 35*).

# Pharmacology

## *Experimental pharmacology*

### Effects on the prostate

Intraperitoneal administration of a lipophilic trunk bark extract (10 mg/kg body weight) daily for 20 days enhanced the secretory activity of the prostate and seminal vesicles in castrated rats, and antagonized the activity of testosterone on these glands. However, in rats which were castrated and adrenalectomized, the extract potentiated the effects of testosterone on both the prostate and seminal vesicles and also increased the concentration of pituitary gonadotropins

(*36*). Intragastric administration of a lipophilic extract of the trunk bark to rats (2 mg/kg body weight) daily for 20–50 days stimulated the secretory activity of the prostate and prevented the development of prostate hyperplasia induced by intraperitoneal injection of human prostate adenoma tissue (*37*). Intragastric administration of a lipophilic extract of the crude drug to rats (100 mg/kg body weight) daily for 3 days also increased prostate secretions (*38*).

### Hormonal activity

Intragastric administration of a lipophilic extract of the trunk bark to ovariectomized mice (150 mg/kg body weight) inhibited estrogen binding (*39*). Intragastric administration of a methylene chloride extract of the trunk bark to male mice inhibited the activity of 5α-reductase ($ED_{50}$ 0.78 mg/ml). The same extract also inhibited the activity of aromatase and 5α-reductase in vitro ($IC_{50}$ 0.98 and 0.78 mg/ml, respectively) (*39*). In another study, however, a lipophilic extract only marginally inhibited the activity of 5α-reductase from human prostate cells in vitro at a concentration of 63 μg/ml (*40*).

### Anti-inflammatory activity

Intragastric administration of a lipophilic extract of Cortex Pruni Africanae (400 mg/kg body weight) suppressed carrageenan-induced footpad oedema in rats. Intraperitoneal administration of the extract to rats (100 mg/kg body weight) also reduced the increase in vascular permeability caused by histamine (*41*). A lipophilic extract of the trunk bark inhibited the production of 5-lipoxygenase metabolites, such as chemotactic leukotrienes, in human polymorphonuclear cells stimulated by the calcium ionophore A23187 (*42*, *43*).

### Antispasmodic activity

A lipophilic extract of the crude drug administered intragastrically to rats inhibited spasms of the bladder induced by electroshock, phenylephrine, adenosine triphosphate and carbachol (*44*). A reduction in carbachol-induced spasms of the bladder was observed after intragastric administration of a lipophilic extract of the crude drug to guinea-pigs (*36*). Intragastric administration of a lipophilic extract of the trunk bark to rabbits (100 mg/kg body weight) prevented the development of contractile dysfunction induced by partial obstruction of the bladder (*45*). A lipophilic extract of the crude drug improved the contractility of the detrusor muscle of the bladder in old rats (*46*).

### Inhibition of cell proliferation

A chloroform extract of the crude drug (10 μg/ml) significantly inhibited proliferation of Swiss 3T3 mouse fibroblasts induced by basic fibroblast growth factor and epidermal growth factor in vitro ($P < 0.05$) (*47*, *48*). DNA synthesis in rat prostatic fibroblasts, induced by insulin-like growth factor, epidermal growth factor, 12-*O*-tetradecanoyl phorbol-13-acetate or basic fibroblast

growth factor, was inhibited in vitro by a 95% ethanol extract of the trunk bark ($IC_{50}$ 12.4, 12.6, 4.5 and 7.7 µg/ml, respectively) (*49*).

### Toxicity

In acute and chronic toxicity studies in mice and rats, no adverse reactions or fatalities were observed after intragastric administration of a single dose of a lipophilic extract of the trunk bark (1–6 g/kg body weight in mice and 1–8 g/kg body weight in rats). No adverse reactions were observed in mice and rats after chronic intragastric administration of the extract (60 and 600 mg/kg body weight, respectively, daily for 11 months) (*2*).

## Clinical pharmacology

### *Benign prostatic hyperplasia*

### Placebo-controlled clinical trials

Eleven double-blind, placebo-controlled studies assessed the effects of an oral lipophilic extract of Cortex Pruni Africanae in the symptomatic treatment of 717 men with mild to moderate BPH (*22–28, 30, 31, 33, 34*). The number of patients in each study ranged from 14 to 255, and the dosage of the trunk bark extract was 75–200 mg daily for at least 6 weeks. Eight studies measured maximum urinary flow and 10 studies measured daytime and night-time polyuria (*22–26, 28, 30, 31, 33, 34*). One study also included comparison with a combination of the trunk bark extract and medroxyprogesterone acetate (*34*). Seven trials reported a significant improvement in maximum urinary flow following treatment with the extract, as compared with placebo (*22–26, 28, 31*). However, in one study with only a small number of patients, no beneficial urodynamic effects were seen (*27*). Ten of these trials also demonstrated significant improvements in the symptoms of nocturia, daytime polyuria, dysuria, and the hesitancy and urgency of micturition, as compared with placebo (*22–26, 28, 30, 31, 33, 34*).

A histological study of prostate tissue biopsies from patients with BPH before and after treatment (75 mg extract daily for 1–3 months) showed that a lipophilic extract of the trunk bark enhanced prostate secretion, but did not reduce the size of the prostate (*50*). A lipophilic extract of the trunk bark also restored the activity of prostate acid phosphatase and the normal levels of total protein secretion from the prostate in patients with abnormally low levels of secretion (*51*).

### *Comparative studies*

Four double-blind studies compared oral administration of a lipophilic extract of the crude drug and docosanol (one of the active constituents of the extract) with an extract of Radix Urticae Urtae, sitosterin, non-steroidal anti-inflammatory drugs and antibiotics (*22, 52, 53*). The total number of patients was 183, with a range of 39–53 patients per study. Patients were treated with either 100 mg docosanol, 100 mg trunk bark extract or varying doses of the compara-

tive drugs. Improvements in postvoid residual volume, nocturia, daytime polyuria and the urgency of micturition were seen in all treatment groups in three studies, with the trunk bark extract appearing to be the most effective (*22, 52, 53*). However, no controlled studies have yet been performed to compare the effects of trunk bark extracts with newer agents (e.g. finasteride or $\alpha_1$-receptor antagonists, such as alfuzosin) for the treatment of BPH symptoms.

### Clinical trials without controls

Fourteen clinical trials without controls demonstrated an improvement of global outcome assessments after oral treatment with a chloroform extract of the trunk bark in 461 men with stage I or II BPH (*54–67*). In four of these studies, a total of 180 patients received 75 mg extract daily for 21 days to 3 months (*54, 56, 64, 66*); in the other 10 studies, a total of 281 patients were treated with 100 mg extract daily for 21 days to 3 months (*55, 57–63, 65, 67*). In all but three studies (*59, 63, 67*), the global outcome was assessed as either improved, good, very good or excellent in over 50% of the patients.

The results of 19 clinical trials without controls involving 849 men with BPH (18–59 patients per study) demonstrated an objective improvement in their symptoms following treatment with a lipophilic extract of the trunk bark (*53, 68–85*). Patients were treated daily with either 75 mg (116 patients), 75–100 mg (20 patients), 100 mg (523 patients), 150 mg (42 patients) or 200 mg extract (148 patients) for 20–160 days. Improvements in nocturia, daytime polyuria, postvoid residual volume and mean maximum urinary flow rate were observed in over 50% of patients in 14, eight, seven and four studies, respectively. Other symptoms such as dysuria, and hesitancy and urgency of micturition also improved (*44*).

A large open-label study assessed improvements in urodynamic parameters in 500 men with BPH after daily treatment with a lipophilic extract of the bark for over 5 years (doses not specified). Improvements in dysuria, daytime polyuria and nocturia were observed in over 68% of patients, and improvements in urinary flow rate and volume were reported in over 61% (*32*). The greatest improvements were observed in patients with moderate symptoms, who did not have a prominent median lobe of the prostate, and whose baseline postvoid residual volume was less than 100 ml (*32, 44*). An improvement in prostate secretion was also reported, but only in the absence of prostate infection (*38*).

A multicentre study without controls assessed the efficacy and safety of treatment with a trunk bark extract (50 mg) twice daily for 2 months in 85 men with symptoms of BPH (neither the extract nor the stage of BPH was described). Subjective assessment of the outcomes was made using the International Prostate Symptom Score (IPSS) and the Quality of Life score (QL), and urine flowmetry was used for objective evaluation. After treatment, the IPSS and QL improved significantly ($P < 0.001$) by 40% and 31%, respectively. Nocturnal frequency was also significantly reduced by 32% ($P < 0.001$) (*55*).

## Contraindications

Cortex Pruni Africanae is contraindicated in cases of known allergy to plants of the Rosaceae family. It is also contraindicated during pregnancy and lactation and in children under the age of 12 years because of its effects on androgen and estrogen metabolism (*39*, *86*).

## Warnings

Cortex Pruni Africanae relieves the symptoms associated with BPH, but does not have an effect on the size of the prostate. If symptoms worsen or do not improve, or if blood appears in the urine or acute urinary retention occurs, contact a physician.

## Precautions

### *Carcinogenesis, mutagenesis, impairment of fertility*

A lipophilic extract of Cortex Pruni Africanae had no effect on fertility in male rats and rabbits at doses up to 80 mg/kg body weight daily (*44*). No mutagenic or clastogenic activity has been observed in vitro or in vivo (*44*).

### *Pregnancy: teratogenic effects*

See Contraindications. There is no therapeutic rationale for the use of Cortex Pruni Africanae during pregnancy.

### *Pregnancy: non-teratogenic effects*

See Contraindications. There is no therapeutic rationale for the use of Cortex Pruni Africanae during pregnancy.

### *Nursing mothers*

See Contraindications. There is no therapeutic rationale for the use of Cortex Pruni Africanae during lactation.

### *Paediatric use*

See Contraindications. There is no therapeutic rationale for the use of Cortex Pruni Africanae in children.

### *Other precautions*

No information available on general precautions or precautions concerning drug interactions; or drug and laboratory test interactions.

## Adverse reactions

Data from clinical studies show that a lipophilic extract of Cortex Pruni Africanae is well tolerated in humans. A few cases of minor transient gastro-

intestinal side-effects, such as diarrhoea, gastric pain and nausea, were reported in two clinical trials (*22, 23*), and single cases of constipation, dizziness and visual disturbance were also reported (*23*).

## Dosage forms

Lipophilic extract of the crude drug (*1, 2*). Store in a cool, dry place.

## Posology

(Unless otherwise indicated)
Daily dosage: 75–200 mg lipidosterolic extract of the crude drug, in divided doses. To minimize gastrointestinal disturbances, take with food or milk.

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# Cortex Rhamni Purshianae

## Definition

Cortex Rhamni Purshianae consists of the dried bark of *Rhamnus purshiana* D.C. (Rhamnaceae) (*1–5*). Cascara (*2*) and Cascara Sagrada (*5*) are also official names of the drug.

## Synonyms

*Frangula purshiana* (D.C.) A. Gray ex J.C. Cooper (*3, 5*), *Rhamnus purshianus* D.C. (*4*). Although the species name in the British, French, German and European pharmacopoeias is given as *purshianus*, the correct species name is *purshiana* according to the *International code of botanical nomenclature* (Tokyo code) (*4*; J. Morley, personal communication, 1998).

## Selected vernacular names

Amerikanischen Faulbaum, bear wood, bitter bark, cascara bark, cascararinde, chittem bark, cortex cascara sagradae, écorce de cascara, purshiana bark, quishron moquaddas, Rhamnus, sacred bark (*1, 6–8*).

## Geographical distribution

Indigenous to south-western Canada and the Pacific north-west of the United States of America (*8–10*).

## Description

A tree, 4–10 m high, with reddish-brown bark and hairy twigs. Leaves petiolate, elliptical, acuminate, serrulate, or sometimes entire, with 10–15 pairs of veins, dull green upper surface and pubescent underside. Inflorescence an axillary umbellate cyme of small greenish flowers. Fruit a turbinate, purplish-black drupe, about 8 mm long, composed of 3 indehiscent cocci (*8*).

## Plant material of interest: dried bark

The fresh bark contains free anthrones and must be dried for at least 1 year or artificially aged by heat or aeration before therapeutic use (*1, 5, 8*).

### General appearance

Occurs in quills, slightly channelled or nearly flat pieces; usually 1–5 mm thick, usually varying greatly in length (up to 20 cm) and width (up to 2 cm). Outer surface brown, purplish-brown or brownish-red, usually more or less completely covered by a whitish coat of lichens, epiphytic moss and foliaceous liverwort; shows occasional lenticels that are orientated transversally. Inner surface light yellow to reddish-brown or almost black, with fine longitudinal striations; turns red when treated with dilute alkali (Bornträger's test). Fracture short and granular in outer part and somewhat fibrous in the inner part (*1*, *3*, *5*).

### Organoleptic properties

Odour: faint, but characteristic; taste: bitter, nauseous and persistent (*1*, *11*).

### Microscopic characteristics

Cork frequently bearing dense masses of lichen tissues, and formed of 10 or more rows of small, flattened, thin-walled cells with yellowish-brown contents. Cortex narrow, yellowish-grey, consisting of a few layers of collenchyma and several layers of parenchyma, containing starch granules and scattered cluster crystals of calcium oxalate; showing numerous scattered, bright, ovoid groups of sclereids, usually encircled by cells containing prismatic crystals of calcium oxalate. Phloem brownish-yellow, traversed by numerous wavy medullary rays (1–5 cells wide and 15–25 cells deep); consists of alternating bands of lignified fibres, surrounded by crystal sheath containing prismatic crystals of calcium oxalate, and of soft sieve tissue and parenchyma with brown walls; contains scattered cluster crystals of calcium oxalate and starch grains; each fibre 8–15 μm in diameter. Groups of sclereids also found in outer part of phloem; sclereids possess thick, stratified, pitted walls. Parenchyma may contain yellow substance which turns crimson with dilute alkali (Bornträger's test) (*1*, *5*).

### Powdered plant material

Yellowish-brown to dusky yellowish-orange. Bundles of partly lignified phloem fibres accompanied by crystal sheaths containing prismatic crystals of calcium oxalate; groups of sclereids accompanied by crystal sheaths; cluster crystals of calcium oxalate, 5–20 μm, occasionally up to 45 μm, in diameter; some parenchymatous cells contain yellow substance which turns crimson when treated with dilute alkali (Bornträger's test); cork cells and frequently epiphytes—latter may be liverworts (entire or in fragments, having a lamina one cell thick without a midrib and composed of isodiametric cells) or mosses (having a lamina 1 cell thick composed of elongated cells and possessing a midrib several cells thick); starch grains spheroid, up to 8 μm in diameter (*1*, *3*, *5*).

## General identity tests

Macroscopic, microscopic and microchemical (Bornträger's test) examinations (*1*, *3*, *5*) and thin-layer chromatography for characteristic hydroxyanthracene glycosides (*3*, *12*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

### *Foreign matter*

Not more than 1% (*3*).

### *Total ash*

Not more than 7% (*1*, *3*).

### *Water-soluble extractive*

Not less than 23% (*1*).

### *Loss on drying*

Not more than 10% (*3*).

### *Pesticide residues*

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

### *Heavy metals*

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

### *Radioactive residues*

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

### *Other purity tests*

Chemical, acid-insoluble ash, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

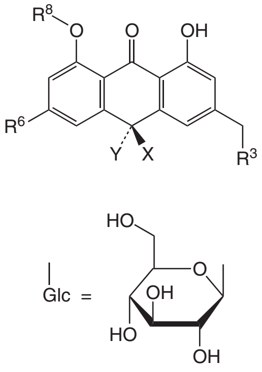
## Chemical assays

Contains not less than 8.0% hydroxyanthracene glycosides of which not less than 60% consists of cascarosides, both calculated as cascaroside A. Quantitative analysis is performed by spectrophotometry at 515 nm (*3, 5*). A high-performance liquid chromatography method for the quantitative analysis of cascarosides has been reported (*16*).

## Major chemical constituents

The active constituents are hydroxyanthracene glycosides (6–9%). Of these, 70–90% are C-10 glycosides, with the 8-*O*-glycosides, aloins A and B, and 11-desoxyaloins A and B (chrysaloins A and B) accounting for 10–30%. The diastereoisomeric pairs, cascarosides A and B and cascarosides C and D and cascarosides E and F constitute 60–70% of the total *O*-glycosides. Other major hydroxyanthracene glycosides (10–20%) include the hydroxyanthraquinones, chrysophanol-8-*O*-glucoside and aloe-emodin-8-*O*-glucoside (*7, 17–19*).

In the fresh bark, anthraquinones are present in the reduced form, and are converted by oxidation from their corresponding parent anthraquinone glycosides during drying and storage (*10*). The structures of the major anthracene glycosides are presented below.



β-D-glucopyranosyl

| | X | Y | $R^3$ | $R^6$ | $R^8$ |
|---|---|---|---|---|---|
| aloin A | Glc | H | OH | H | H |
| aloin B | H | Glc | OH | H | H |
| cascaroside A | Glc | H | OH | H | Glc |
| cascaroside B | H | Glc | OH | H | Glc |
| cascaroside C | Glc | H | H | H | Glc |
| cascaroside D | H | Glc | H | H | Glc |
| cascaroside E | Glc | H | H | OH | Glc |
| cascaroside F | H | Glc | H | OH | Glc |
| chrysaloin A | Glc | H | H | H | H |
| chrysaloin B | H | Glc | H | H | H |

## Medicinal uses

### *Uses supported by clinical data*

Short-term treatment of occasional constipation (*8, 17, 20, 21*).

### *Uses described in pharmacopoeias and in traditional systems of medicine*

As a cathartic (*1*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

Internally for treatment of diabetes and externally for skin irritations (*6*).

## Pharmacology

### *Experimental pharmacology*

#### Laxative effects

The laxative effects of Cortex Rhamni Purshianae are due primarily to the anthraquinone glycosides and cascarosides A–D (*7, 22*). After oral administration of Cortex Rhamni Purshianae, the hydroxyanthracene glycosides are not absorbed in the upper intestine, but are hydrolysed in the colon by intestinal bacteria to form the pharmacologically active metabolites. These metabolites are partially absorbed in the colon and act as a stimulant and irritant to the gastrointestinal tract, as does senna (*21, 23–25*). The mechanism of action, similar to that of senna, is twofold. Firstly, there is stimulation of colonic motility, resulting in increased propulsion and accelerated transit of faeces through the colon (which reduces fluid absorption from the faecal mass). Secondly, there is an increase in paracellular permeability across the colonic mucosa, probably due to inhibition of sodium/potassium-transporting adenosine triphosphatase or inhibition of chloride channels (*23, 26*). The increased permeability results in increased water content in the colon (*21, 26*).

The laxative effect of Cortex Rhamni Purshianae is not generally observed until 6–8 hours after oral administration. Hydroxyanthracene glycosides are excreted predominantly in the faeces but are also excreted to some extent in urine, producing an orange colour; anthrones and anthranols will also pass into breast milk (*23*).

#### Toxicity and overdose

As with other anthraquinone laxatives, the major symptoms of overdose are intestinal pain and severe diarrhoea with consequent loss of fluid and electrolytes (*27*). Treatment of overdoses should be supportive with generous amounts of fluid. Electrolyte levels should be monitored, particularly those of potassium. This is especially important in children and the elderly (*27*).

## Clinical pharmacology

None.

## Contraindications

Cortex Rhamni Purshianae should not be administered to patients with intestinal obstruction and stenosis, atony, inflammatory diseases of the colon (such as ulcerative colitis, irritable bowel syndrome, Crohn disease), appendicitis,

severe dehydration with water and electrolyte depletion, or chronic constipation (*20, 24, 27*). As with other stimulant laxatives, Cortex Rhamni Purshianae is contraindicated in patients with cramps, colic, haemorrhoids, nephritis or any symptoms of undiagnosed abdominal disorders such as pain, nausea or vomiting (*27*). Owing to the pronounced action on the large intestine and insufficient toxicological investigations, Cortex Rhamni Purshianae and other anthranoid laxatives should not be administered to pregnant women (*28, 29*). As anthranoid metabolites may appear in breast milk, Cortex Rhamni Purshianae should not be used during lactation, since there are insufficient data to assess potential pharmacological effects in the breastfed infant (*29*). Use of Cortex Rhamni Purshianae in children under 10 years is contraindicated (*20*).

## Warnings

Products containing Cortex Rhamni Purshianae should only be used if no effect can be obtained through a change of diet or by the use of bulk-forming laxatives. Patients should also be warned that certain constituents of the bark are excreted by the kidney and may colour the urine orange, which is harmless. Cortex Rhamni Purshianae and other stimulant laxatives should not be used in patients with abdominal pain, nausea or vomiting. The use of stimulant laxatives for longer than 2 weeks requires medical supervision. Rectal bleeding or failure to have a bowel movement after taking a laxative may indicate a serious condition. Chronic use may result in aggravation of constipation with laxative dependence, a need for increased dosages and disturbances of water and electrolyte balance (e.g. hypokalaemia). Chronic use may also lead to colonic dysfunction (atonicity) and melanotic pigmentation of the colonic mucosa (pseudomelanosis coli), which is harmless. Laxative abuse resulting in diarrhoea and consequent fluid and electrolyte losses (mainly of potassium) may cause albuminuria, haematuria, and cardiac and neuromuscular dysfunction. Neuromuscular dysfunction may arise particularly in the case of concomitant use of cardiotonic glycosides (e.g. digoxin, digitalis or strophanthin), diuretics, corticosteroids or liquorice root (*27*).

## Precautions

### General

Cortex Rhamni Purshianae and other laxatives containing anthraquinone glycosides should not be used continuously for longer than 1–2 weeks, because of the risk of electrolyte imbalance (*27*).

### Drug interactions

Increased intestinal transit time may result in reduced absorption of orally administered drugs (*30*). Electrolyte imbalances, such as hypokalaemia, may potentiate the effects of cardiotonic glycosides (e.g. digoxin, digitalis or

strophanthin). Hypokalaemia resulting from long-term laxative abuse can also potentiate the effects of antiarrhythmic drugs (e.g. quinidine) that change sinus rhythm by affecting potassium channels. Hypokalaemia caused by drugs such as thiazide diuretics, adrenocorticosteroids or liquorice root may be enhanced, and electrolyte imbalance may be aggravated (*21*).

### *Drug and laboratory test interactions*

Anthranoid metabolites may not be detectable in faeces or urine by standard methods. Thus faecal excretion measurements may not be reliable (*30*). Urinary excretion of certain anthranoid metabolites may cause discoloration of the urine which is not clinically relevant, but may cause false-positives in urinary urobilinogen tests and in estrogen measurements using the Kober procedure (*31*).

### *Carcinogenesis, mutagenesis, impairment of fertility*

Although chronic use of anthranoid-containing laxatives has been hypothesized to play a role in colorectal cancer, no causal relationship has been demonstrated (*32–35*).

No specific data on carcinogenicity or mutagenicity are available for Cortex Rhamni Purshianae or the cascarosides. Data for aloin derived from aloe indicate no genotoxic risk. Emodin derived from aloe showed both positive and negative results in vitro, but was negative in vivo. Emodin was mutagenic in the *Salmonella*/microsome assay, but gave inconsistent results in gene mutation assays (V 79). It showed positive results in the test for unscheduled DNA synthesis with primary rat hepatocytes, but negative results in the sister chromatid exchange assay (*20*).

### *Pregnancy: teratogenic effects*

See Contraindications. Administration of aloin A to rats at doses up to 200 mg/kg body weight had no embryotoxic, teratogenic or fetotoxic effects (*36*).

### *Pregnancy: non-teratogenic effects*

See Contraindications.

### *Nursing mothers*

See Contraindications.

### *Paediatric use*

See Contraindications.

## Adverse reactions

Single doses of Cortex Rhamni Purshianae may result in cramp-like discomfort of the gastrointestinal tract, which may require a reduction of dosage (*21*).

Overdose can lead to colicky abdominal spasms and pain, as well as the formation of thin, watery stools.

Long-term laxative abuse may lead to electrolyte imbalance (hypokalaemia and hypocalcaemia), metabolic acidosis, malabsorption of nutrients, weight loss, albuminuria and haematuria (*37, 38*). Weakness and orthostatic hypotension may be exacerbated in elderly patients when stimulant laxatives are repeatedly used. Secondary aldosteronism may occur after prolonged use due to renal tubular damage. Steatorrhoea and protein-losing gastroenteropathy with hypoalbuminaemia have also been reported after long-term laxative abuse (*39*). Pseudomelanosis coli has been observed in individuals taking anthraquinone laxatives for extended time periods (*27, 38*). The pigmentation is harmless and usually reversible within 4–12 months after the drug is discontinued (*38*). Conflicting data exist on other toxic effects after long-term use such as intestinal-neuronal damage (*38, 40*). In incontinent patients using anthranoid laxatives, prolonged exposure of the skin to faeces may cause skin damage (*41*).

Use of the fresh bark of *Rhamnus purshiana* may cause severe vomiting, with possible abdominal spasms (*23*). One case of occupational asthma and rhinitis has been reported (*42*).

## Dosage forms

Finely cut crude drug, powder, dried extracts, extract (*5*), fluidextract (*5*), other liquid and solid preparations (*5, 7*). Store in a tightly sealed, light-resistant container (*1, 3*).

## Posology

The correct dosage for the treatment of occasional constipation is the smallest dosage necessary to maintain a soft stool. Daily dosage: 0.3–1.0 g crude drug in a single dose (*20*); all preparations standardized to contain 20–30 mg of hydroxyanthracene derivatives calculated as cascaroside A; taken at bedtime, or in two divided doses, one in the morning and one at bedtime (*20, 21*).

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# Flos Sambuci

## Definition

Flos Sambuci consists of the dried flowers of *Sambucus nigra* L. (Caprifoliaceae) (*1–3*).

## Synonyms

*Sambucus arborescens* Gilib., *S. medullina* Gilib., *S. vulgaris* Lam. (*4*).

## Selected vernacular names

Aalhornblüten, aghti, agti, American elder bailasan, black elder, bodzavirág, bombardie, boumbardelia, boumbardier, bourtree flower, couloubrignier, elderberry, elder flowers, European elder, fiore di sambuco, fleurs de sureau, Fliederblüten, flor de sabugeiro, flores de sauco, flores sambuci, flos sambuci nigra, Holderblüten, Hollerblüten, Holunderblüten, Hüschenblumen, kabiu sabugah, Kalikenblumen, Khaman kabiv sabubah, okkez sidi musa, patlanguc, petadou, sabugeiro, sahuquier, sahus sambequie, sambuc, sambuco, sammuch, sammuco, sauci, saucio, sauco, sauguer, seic, seiyouniwatoko, sultanotu, sureau, sureau noir, sweet elder (*4–8*).

## Geographical distribution

Indigenous to North Africa, North America, western and central Asia and Europe (*6*, *7*).

## Description

A shrub growing in moist soil with stems up to 4 m high; contains abundant white pith. Leaves imparipinnate with 5–11 oblong, glabrous leaflets, the lower leaves often 3-lobed. Inflorescence a flat compound cyme. Flowers small, urn-shaped, white, each with 5 minute calyx lobes; corolla 5-cleft gamopetalous, 5 stamens and a tricarpellate pistil with 3 stigmas. Fruits black-purple, edible, berry-like drupes (*6*).

## Plant material of interest: dried flowers

### *General appearance*

Inflorescence a flat compound cyme. Flowers white, up to 5 mm in diameter, has 3 small bracts (visible with a hand lens) and may have a peduncle. Calyx

minute, 5-lobed; corolla light yellow, with 5 broadly oval petals fused at their bases into a tube, 5 yellow stamens with short filaments and lemon-yellow anthers, and a trilocular inferior ovary; ovary bears a short style with 3 obtuse stigmata; filaments of the 5 stamens alternate with the petals. Corolla often isolated or fused to base of the stamens (*1*, *2*).

### Organoleptic properties

Odour: strong, characteristic, aromatic; taste: mucilaginous, sweet but slightly bitter (*1*, *9*).

### Microscopic characteristics

Cells of upper epidermis of sepals polygonal with faintly striated cuticle; cells of lower epidermis sinuous-walled with strongly striated cuticle and scattered, rounded, anomocytic stomata; unicellular marginal teeth rounded at the apex occur in the basal region of sepal. Cells of upper epidermis of petals polygonal with slightly thickened, beaded walls and striated cuticle; cells of lower epidermis distinctly sinuous with large, rounded, anomocytic stomata. Numerous small globules of essential oil in the epidermis of sepals and petals. Mesophyll of sepals and petals contains idioblasts of numerous small, sandy crystals of calcium oxalate. Fibrous layer of anthers with characteristic thickening and beading on walls; pollen grains subspherical, 17–24 μm in diameter, with smooth exine, 3 distinct pores and 3 furrows (*1*).

### Powdered plant material

Greenish-yellow. Numerous spherical, sometimes ellipsoidal, pollen grains up to 30 μm in diameter, with 3 germinal pores and very finely pitted exine; calyx epidermal cells with a striated cuticle and occasional unicellular marginal teeth from basal region; corolla fragments with numerous small globules of essential oil; cells of corolla upper epidermis with slightly thickened, beaded walls and striated cuticle; mesophyll cells of sepals and petals with idioblasts containing numerous sandy crystals of calcium oxalate (*2*).

## General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for constituent phenolic acids and flavonoids (*2*).

## Purity tests

### Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

### Foreign organic matter

Not more than 8% fragments of coarse pedicels and other foreign matter; not more than 15% discoloured, brown flowers (*2*).

### Total ash

Not more than 10% (*1*, *2*).

### Acid-insoluble ash

Not more than 2% (*1*).

### Water-soluble extractive

Not less than 25% (*1*).

### Loss on drying

Not more than 10% (*2*).

### Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*) and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

### Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

### Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

### Other purity tests

Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

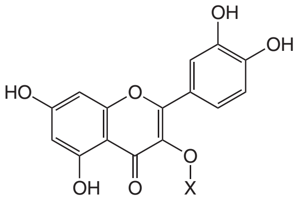
## Chemical assays

Contains not less than 0.80% flavonoids, calculated as isoquercitrin, as determined by spectrophotometry at 425 nm (*2*).

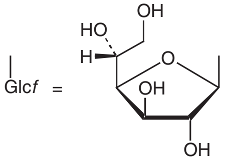
## Major chemical constituents

The major characteristic constituents (up to 3.0%) are the flavonoids (kaempferol, astragalin, quercetin, rutin, isoquercitrin, hyperoside). Other

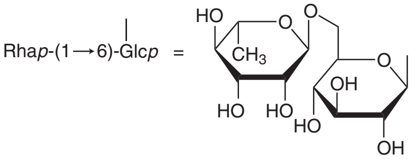
major secondary metabolites include about 1% triterpenes (α- and β-amyrin, ursolic acid, oleanolic acid), about 1% sterols (β-sitosterol, campesterol, stigmasterol), about 3% phenolic acids and their corresponding glycosides (chlorogenic, ferulic, caffeic and *p*-coumaric acids), and up to 0.15% essential oil (*4, 5, 7, 13*). The structures of the representative major constituents are presented below.




quercetin X = H
isoquercitrin X = Glc*f*
rutin X = Rha*p*-(1→6)-Glc*p*

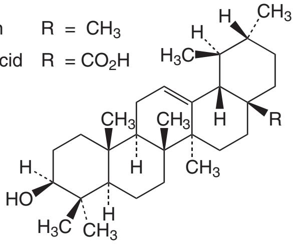


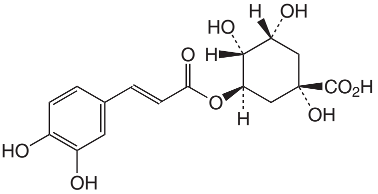

β-D-glucofuranosyl




*O*-6-deoxy-α-L-mannopyranosyl-(1→6)-β-D-glucopyranosyl

α-amyrin R = $CH_3$
ursolic acid R = $CO_2H$




chlorogenic acid

## Medicinal uses

### *Uses supported by clinical data*

None.

### *Uses described in pharmacopoeias and in traditional systems of medicine*

As a diaphoretic for treatment of fever and chills, and as an expectorant for treatment of mild inflammation of the upper respiratory tract. Also for symptomatic treatment of the common cold (*1, 7, 14*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of conjunctivitis, constipation, diabetes, diarrhoea, dry skin, headaches and rheumatism (*5, 13, 15*).

# Pharmacology

## *Experimental pharmacology*

### Anti-inflammatory activity

An 80% ethanol extract of Flos Sambuci had moderate anti-inflammatory activity in rats: it inhibited carrageenan-induced footpad oedema by 27%. The extract was administered intragastrically (100 mg/kg body weight) 1 hour prior to administration of carrageenan. The control drug, indometacin (5 mg/kg body weight) inhibited carrageenan-induced footpad oedema by 45% (*16*). Intraperitoneal administration of an unsaponifiable fraction of the flowers to mice moderately enhanced phagocytosis at a dose of 0.5 ml/animal (*17*). A 100% methanol extract of the flowers inhibited the biosynthesis of the inflammatory cytokines interleukin-1α, interleukin-1β and tumour necrosis factor-α at a concentration of 30 μg/ml in human peripheral mononuclear cells in vitro (*18*).

### Diuretic activity

Intragastric administration of an infusion of the flowers (20 ml/kg body weight) or of a potassium- and flavonoid-rich extract of the flowers had a diuretic effect in rats which was greater than that observed with theophylline (5 mg/kg body weight) (*19*).

## *Clinical pharmacology*

### Diaphoretic activity

Flos Sambuci is reported to increase the response of the sweat glands to heat stimuli (*7, 20, 21*), and increase diaphoresis in healthy subjects (*7, 21*).

# Contraindications

No information available.

# Warnings

No information available.

# Precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Flos Sambuci should not be administered during pregnancy or lactation or to children without medical supervision.

# Adverse reactions

No information available.

## Dosage forms

Crude drug for decoctions and infusions (crude drug also available in tea bags); as a component of multi-ingredient products (*7*). Store in a well-closed container, protected from light (*2*).

## Posology

(Unless otherwise indicated)
Daily dosage: crude drug 3–5 g as an infusion (preferably taken hot) three times daily; 25% ethanol extract 3–5 ml; tincture (1 : 5 in 25% ethanol) 10–25 ml (*22*).

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# Radix Senegae

## Definition

Radix Senegae consists of the dried roots and root crowns of *Polygala senega* L., *Polygala senega* L. var. *latifolia* Torrey et Gray, or other closely related *Polygala* species (Polygalaceae) (*1–3*).

## Synonyms

*Polygala senegum* L. (*1*), *P. rosea* Steud., *Senega officinalis* Spach (*4*).

## Selected vernacular names

Bambara, bulughâ lon, gizr uththuban, Klapperschlangenwurzel, mountain flax, peuhl, polygala de virginie, racine de polygala, racine de senega, Radix polygalae, Radix polygalae senegae, rattlesnake root, seneca snakeroot, Senegakreuzblume, senega root, senega snakeroot, Senegawurzel, snake root, szenega gyökér, tsuknida, vahulill, virginische Schlangenwurzel, yoruba (*1–3*, *5–7*).

## Geographical distribution

Indigenous to eastern Canada and north-eastern United States of America (*6–8*).

## Description

A perennial herbaceous plant with numerous stems sprouting from a single thick gnarled crown arising from a conical, twisted, branched yellow root. Aerial portion consists of several erect or ascending, smooth stems up to 15–40 cm high, bearing alternate, lanceolate or oblong-lanceolate leaves with serrulate margins. Inflorescence a spike of small, white flowers, which are almost sessile with rounded-obovate wings, concave with a short crested carina (*1*, *7*).

## Plant material of interest: dried roots and root crowns

### *General appearance*

Root crown greyish-brown, wider than the root; diameter of the root crown up to 3 cm, gradually tapering to the tip; surface transversely and longitudinally striated, often shows a more or less distinct decurrent, elongated spiral keel. Forms an irregular head consisting of numerous remains of stems and tightly

packed purplish-brown to red buds. Taproot, 0.5–1.5 cm in diameter and 3–20 cm in length, brown to yellow, occasionally branched, sometimes flexuous, usually without secondary roots, except in the Japanese varieties and species, which contain numerous fibrous branched rootlets. Fracture short and shows a yellowish cortex of varying thickness surrounding a pale central woody area somewhat circular or irregular in shape, depending on the species (*1–3*).

### Organoleptic properties

Odour: characteristic, faint, sweet, slightly rancid or reminiscent of methyl salicylate, sternutatory when in powder form; taste: sweet, subsequently acrid and irritating to the throat (*1–3*).

### Microscopic characteristics

Cork layer consisting of several rows of light-brown cork cells; secondary cortex composed of parenchyma cells and sieve tubes, traversed by medullary rays, 1–3 cells wide. Phelloderm of slightly collenchymatous cells containing droplets of oil. Phloem and xylem arrangement usually normal, especially near the crown, but where a keel is present, it is formed by increased development of phloem; other anomalous secondary development sometimes occurs, resulting in formation of 1 or 2 large wedge-shaped rays in phloem and xylem, the parenchymatous cells of which contain droplets of oil. Xylem usually central, consists of vessels up to 60 µm in diameter associated with numerous thin-walled tracheids and a few small lignified parenchymatous cells. Starch grains and calcium oxalate crystals absent (*1–3*).

### Powdered plant material

Light brown. Longitudinal fragments of lignified tissue made up of pitted tracheids and somewhat larger vessels with numerous bordered pits or with reticulate thickening; yellowish parenchyma and collenchymatous cells containing droplets of oil; occasional fragments of cork and epidermal tissue with stomata and unicellular trichomes from bud scales. Calcium oxalate crystals and stone cells are absent (*1–3*).

## General identity tests

Macroscopic and microscopic examinations (*1–3*), chemical tests and froth formation (*1*, *2*), and thin-layer chromatography for the presence of saponins (3).

## Purity tests

### Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*9*).

### Foreign organic matter
Not more than 2% stems and not more than 1% other foreign matter (*2*).

### Total ash
Not more than 6% (*3*).

### Acid-insoluble ash
Not more than 2% (*1*, *2*).

### Alcohol-soluble extractive
Not less than 30% in 20% alcohol (*2*).

### Loss on drying
Not more than 13% (*2*).

### Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*3*). For other pesticides, see the *European pharmacopoeia* (*3*) and the WHO guidelines on quality control methods for medicinal plants (*9*) and pesticide residues (*10*).

### Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*9*).

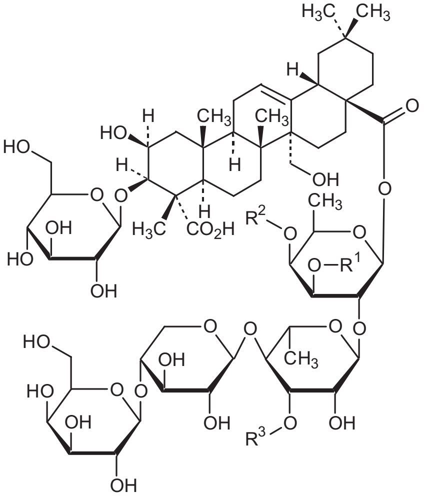
### Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*9*) for the analysis of radioactive isotopes.

### Other purity tests
Chemical, sulfated ash and water-soluble extractive tests to be established in accordance with national requirements.

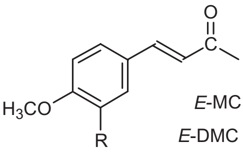
## Chemical assays
Quantitative analysis of triterpene saponins by high-performance liquid chromatography (*11*).

## Major chemical constituents
Methyl salicylate (0.1–0.3%), the compound responsible for the characteristic odour of the drug (*12*). The major reported biologically active constituents are triterpene saponins (6–16%) (*6, 8, 13*). The saponins are 3-glucosides of

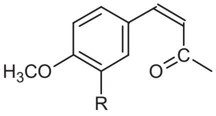
presenegenin, which also contain at C-28 an oligosaccharide chain that has a fucose moiety esterified with 3,4-dimethoxycinnamic or 4-methoxycinnamic acid (*14–16*). The structures of the representative saponins are presented below.



| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| (*E*)-senegasaponin A | H | *E*-MC | Api |
| (*Z*)-senegasaponin A | H | *Z*-MC | Api |
| desacylsenegasaponin A | H | H | Api |
| (*E*)-senegasaponin B | H | *E*-MC | H |
| (*Z*)-senegasaponin B | H | *Z*-MC | H |
| senegin II | H | *E*-DMC | H |
| (*Z*)-senegin II | H | *Z*-DMC | H |
| desacylsenegin II | H | H | H |
| (*E*)-senegin III | Rha | *E*-MC | H |
| (*Z*)-senegin III | Rha | *Z*-MC | H |
| desacylsenegin III | Rha | H | H |

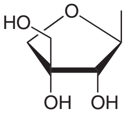


*E*-MC R = H
*E*-DMC R = $OCH_3$



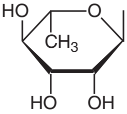
*Z*-MC R = H
*Z*-DMC R = $OCH_3$

Api =



D-*apio*-β-D-furanosyl

Rha =



6-deoxy-α-L-mannopyranosyl

# Medicinal uses

## *Uses supported by clinical data*

None.

## *Uses described in pharmacopoeias and in traditional systems of medicine*

As an expectorant for symptomatic treatment of coughs due to bronchitis, emphysema and catarrh of the upper respiratory tract (*1, 6, 14, 17–19*).

## *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of amenorrhoea, asthma, constipation, rheumatism and snake bites (*5*).

# Pharmacology

## *Experimental pharmacology*

### Expectorant activity

Intragastric administration of a fluidextract of Radix Senegae (0.1–10 ml/kg body weight) enhanced the production of respiratory tract fluid in decerebrate or anaesthetized animals. Three to four hours after administration, the output of respiratory tract fluid increased by up to 173% in cats and 186% in guinea-pigs, but no effect was observed in rabbits (*20*). In another study, administration of a syrup of the root to anaesthetized dogs significantly increased the volume of respiratory tract fluid within 5–30 minutes ($P < 0.001$); after 2 hours, the fluid volume in the treatment group was 0.114 ml as compared with 0.01 ml in control animals treated with saline (*21*). Intragastric administration of a 50% methanol extract of the root (2 g/kg body weight) inhibited stress-induced gastric ulcers in rats by 98.5% (*22*). Intragastric administration of an aqueous suspension of a 50% methanol extract of the root (2 g/kg body weight) to rats reduced congestive oedema by 62% and significantly increased the 24-hour urine volume as compared with control animals ($P < 0.01$) (*23*).

### Effect on blood cholesterol and triglyceride levels

Intraperitoneal administration of an *n*-butanol extract of the root (5 mg/kg body weight) reduced blood triglyceride levels in mice fed a normal diet, and reduced blood cholesterol and triglyceride levels in mice fed a high cholesterol diet (*24*).

### Antihyperglycaemic activity

Intraperitoneal administration of an *n*-butanol extract of the roots (10 mg/kg body weight) reduced blood glucose levels in healthy mice and in mice with streptozocin-induced hyperglycaemia (*25*). Intragastric administration of a saponin fraction of a root extract reduced glucose-induced hyperglycaemia in rats at a dose of 200 mg/kg body weight (*16*). Intraperitoneal administration of a saponin fraction of a root extract (25 mg/kg body weight) significantly increased the plasma levels of adrenocorticotropic hormone, cortisone and glucose in rats ($P < 0.01$) (*26*). Intragastric administration of a 100% methanol extract of the root decreased the absorption of ethanol in rats (500 mg/kg body weight) (*15*).

### Toxicity

The $LD_{50}$ of the root was 17 g/kg body weight after intragastric administration to mice. The $LD_{50}$ of the root bark was 10 g/kg body weight and that of the root core (which had the lowest saponin concentration of the three root samples) was 75 g/kg body weight (*13*).

### *Clinical pharmacology*

**Expectorant activity**

The expectorant activity of the crude drug is due to the constituent saponins which produce local irritation of the mucous membranes of the throat and respiratory tract. This irritation stimulates an increase in bronchial secretions, thereby diluting the mucus, reducing its viscosity and facilitating expectoration (*19–21*, *27*, *28*). Saponins may also reduce the surface tension of mucus, thus reducing its viscosity (*29*). Oral administration of a fluidextract of the root was shown to reduce the viscosity of mucus in patients with bronchiectasis (*17*).

## Contraindications

Pregnancy (See Precautions).

## Warnings

If coughing persists for more than 7 days, seek medical advice. Radix Senegae may exacerbate existing gastrointestinal inflammations such as gastritis or gastric ulcers, and excessive doses may cause vomiting (*30*).

## Precautions

### *Carcinogenesis, mutagenesis, impairment of fertility*

No mutagenic effects of an aqueous or 50% methanol extract of the root were observed in the *Bacillus subtilis* recombination assay or in the microsome reversion assay in *Salmonella typhimurium* strains TA98 and TA100 (*31*).

### *Pregnancy: teratogenic effects*

See Contraindications.

### *Pregnancy: non-teratogenic effects*

Traditional uses for Radix Senegae include its use as an emmenagogue (*5*). As extracts of the root have been shown to stimulate uterine contractions in animal models (*32*), Radix Senegae should not be taken during pregnancy.

## Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; nursing mothers; or

paediatric use. Therefore, Radix Senegae should not be administered during lactation or to children without medical supervision.

## Adverse reactions

Overdose with Radix Senegae preparations may cause nausea, diarrhoea and vomiting due to gastrointestinal upset (*13*). In sensitive individuals, gastro-intestinal upset may occur even at the therapeutic dosage (*33*, *34*).

## Dosage forms

Chopped crude drug for decoctions and extracts (*6*, *18*). Store in a tightly closed container, protected from light and humidity (*3*).

## Posology

(Unless otherwise indicated)
Daily dosage: 1.5–3.0 g crude drug as an infusion or decoction in divided doses (*18*, *35*). A 60% ethanol extract (made slightly alkaline with dilute ammonia): 0.9–3 ml; tincture: 2.5–7.5 g. Equivalent preparations (*18*).

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# Fructus Serenoae Repentis

## Definition

Fructus Serenoae Repentis consists of the dried ripe fruits of *Serenoa repens* (Bartr.) Small. (Arecaceae) (*1–3*).

## Synonyms

*Brahea serrulata* (Michx.) H. Wendl., *Chamaerops serrulata* Michx., *Corypha repens* Bartr., *Sabal serrulata* (Michx.) Nichols, *Sabal serrulata* (Michx.) Nuttall. ex Schult., *Serenoa serrulata* Hook., *Serenoa serrulata* Roem. et Schult., *Serenoa serrulatum* (Michx.) Benth et Hook, *Serenoa serrulatum* Schult. (*1, 3–5*).

## Selected vernacular names

American dwarf palm tree, dwarf palm tree, dwarf palmetto, fan palm, sabal, sabal fructus, Sägepalmenfrüchte, saw palmetto, saw palmetto berries, serenoa (*1, 2, 5, 6*).

## Geographical distribution

Indigenous to the south-east of the United States of America, from South Carolina to Florida (*2, 6*).

## Description

Low scrubby palm growing in sandy soil, with characteristic creeping rhizome, one end of which rises a short distance above ground, surrounded by a dense crown of leaves with saw-like margins. Petioles slender and spinose on edges; blade fan-shaped, with palmate divisions that are slightly cleft at the summit. Inflorescence densely tomentose and shorter than the leaves. Fruit a 1-seeded drupe (*6*).

## Plant material of interest: dried ripe fruits

### *General appearance*

Drupe superior, ellipsoidal, ovoid or somewhat globular, 1.5–3.0 cm long, 1.0–1.5 cm in diameter; dark brown to black with a smooth, dull surface, somewhat oily, with a few large, angular depressions and ridges due to contraction of the

inner layer on drying; summit marked by remains of style; base marked by stem-scars or has remains of stem. Epicarp and sarcocarp together form a thin coriaceous shell enclosing a hard but thin endocarp; endocarp externally reddish-brown and somewhat fibrous, as is inner layer of the sarcocarp; inner layer of endocarp smooth, enclosing an ellipsoidal or ovoid, hard somewhat flattened, anatropous, reddish-brown seed marked on the raphe side by an arillus-like appendage and marked on the opposite side near the end by the micropyle, which forms a slight projection; has a large endosperm of thick-walled parenchyma and a very small embryo at the micropyle (*2*, *3*, *6*).

### Organoleptic properties

Odour: pronounced, aromatic, fruity; taste: sweetish, aromatic, slightly acrid (*6*).

### Microscopic characteristics

Sarcocarp covered by a small-celled, thin-walled epidermis. Outermost layers of pulp wall contain yellowish-brown or brownish-red substances; inner layers have scattered single cells containing brown substances; occasional large, thick-walled, punctate stone cells with wide lumens. Innermost layer of sarcocarp wall consists almost completely of thick-walled, punctate, irregularly shaped stone cells. Outer layer of the seed coat consists of thick-walled large cells; cells in middle layer smaller and thin-walled; cells of innermost layer small and flattened; contents of all seed-coat cells non-punctate brown. Outer endosperm cells radially elongated, coarse-walled and inner cells larger, thick-walled and coarsely punctate. Vascular bundles accompanied by fibres with stigmata which have siliceous solids attached (*3*, *6*).

### Powdered plant material

Yellowish-brown. Fragments of sarcocarp, the cells of which contain yellowish-brown or brownish-red amorphous substances; whitish fragments of endosperm, the cell walls considerably thickened and with large pores; occasional stone cells, nearly colourless, more or less tabular or irregular in shape, up to 140 µm in length, with walls about 15 µm thick, showing numerous simple or branching pores (*2*, *6*).

## General identity tests

Macroscopic and microscopic examinations (*2*, *3*, *6*), and thin-layer chromatography (*7*).

## Purity tests

### Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*8*).

### *Foreign organic matter*
Not more than 2% (*2*, *3*).

### *Total ash*
Not more than 5% (*3*).

### *Acid-insoluble ash*
Not more than 1% (*2*, *3*).

### *Water-soluble extractive*
Not less than 8% (*2*, *3*).

### *Loss on drying*
Not more than 12% (*3*).

### *Pesticide residues*
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*9*). For other pesticides, see the *European pharmacopoeia* (*9*), and the WHO guidelines on quality control methods for medicinal plants (*8*) and pesticide residues (*10*).

### *Heavy metals*
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*8*).

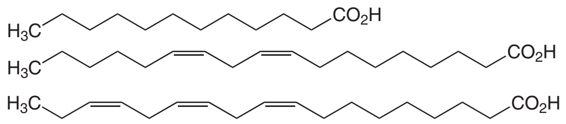
### *Radioactive residues*
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*8*) for the analysis of radioactive isotopes.

### *Other purity tests*
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

## Chemical assays
Quantitation of fatty acids, both free and as their corresponding ethyl esters, by gas chromatography. The total fatty acid content is not less than 9.0%, and the amounts of individual fatty acids are not less than 3.0% oleic, 2.0% lauric, 1.2% myristic, 1.1% palmitic, 0.4% linoleic, 0.2% caphoic, 0.2% caprylic, 0.2% capric, 0.1% palmitoleic, 0.1% stearic and 0.1% linolenic acids (*3*).

## Major chemical constituents

The major constituents are free fatty acids and their corresponding ethyl esters; sterols and lipids. The primary fatty acid constituents include oleic, lauric, myristic, palmitic, linoleic, caphoic, caprylic, capric, palmitoleic, stearic and linolenic acids (*5*, *11*, *12*). The major sterols include β-sitosterol, stigmasterol and daucosterol (*13*). The lipids consist of triglycerides of fatty acids. The structures of some of the free fatty acids are presented below.




## Medicinal uses

### *Uses supported by clinical data*

Treatment of lower urinary tract symptoms (nocturia, polyuria, urinary retention) secondary to BPH stages I and II, as defined by Alken (*1*, *4*, *14–33*), in cases where diagnosis of prostate cancer is negative.

### *Uses described in pharmacopoeias and in traditional systems of medicine*

As a diuretic and to treat an enlarged prostate (*2*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

As an aphrodisiac, a sedative and a nutritional tonic, as well as for the treatment of bronchitis, cystitis, dysmenorrhoea, sore throat and the common cold (*5*).

## Pharmacology

### *Experimental pharmacology*

#### Antispasmodic activity

Both lipid and saponifiable fractions of Fructus Serenoae Repentis reduced norepinephrine-induced contractions in vitro of rat aorta ($IC_{50}$ 0.53 and 0.50 mg/ml, respectively), as well as potassium chloride-induced contractions of rat uterus ($EC_{50}$ 0.35 and 0.43 mg/ml, respectively) (*34*). A 90% ethanol extract of the fruit reduced vanadate-induced contractions of the rat uterus ($EC_{50}$ 11.41 μg/ml). Norepinephrine-induced contractions of rat deferential duct, and potassium chloride-induced contractions of guinea-pig ileum and bladder smooth muscle tissue were reduced by the addition of a 90% ethanol extract of the fruit (0.33 and 0.15 mg/ml, respectively) (*35*).

### Anti-inflammatory activity

Intragastric administration of an ethanol extract of the fruit to rats (5.0 g/kg body weight) inhibited carrageenan-induced footpad oedema (*36*). External application of a 90% ethanol extract of the fruit (500 μg) to mice inhibited croton oil-induced ear oedema by 42% (*37*).

Intragastric administration of an *n*-hexane extract of the fruit to rats (10 ml/kg body weight) decreased capillary permeability induced by histamine, compound 48/80 and dextran, and generalized oedema induced by dextran (*38*). A carbon dioxide (supercritical) extract of the fruit inhibited cyclooxygenase and 5-lipoxygenase in vitro ($IC_{50}$ 28.1 and 18.0 μg/ml, respectively) (*39*). A lipidosterolic extract of the fruit inhibited the in vitro production of leukotriene $B_4$ in human polymorphonuclear neutrophils stimulated with the calcium ionophore A23187 (*40*). An ethanol extract of the fruit also suppressed A23187-stimulated synthesis of leukotriene $B_4$ ($IC_{50}$ 8.3 μg/ml) and thromboxane $B_2$ ($IC_{50}$ 15.4 μg/ml) in rat peritoneal leukocytes in vitro (*37*).

### Immunostimulatory activity

Intraperitoneal administration of a polysaccharide fraction, isolated from an aqueous extract of the fruit, to mice (10 mg/kg body weight) had immunostimulant activity, as measured by the colloidal carbon clearance test (*41*). An increased rate of phagocytosis by human polymorphonuclear leukocytes was observed in cells treated with a polysaccharide fraction of the extract (10 μg/ml) (*41*).

### Anti-gonadotropic effects

*n*-Hexane extracts of the fruit had anti-androgenic and anti-estrogenic activity in vitro (*42–47*). Dihydrotestosterone and testosterone uptake by cytosolic androgen receptors of human foreskin and other tissues was inhibited by 40.9% and 41.9%, respectively, after treatment of the tissues with the extract (*42*). In another study, the binding of [$^3$H]dihydrotestosterone to both cytosolic and nuclear androgen receptors in cultured human foreskin fibroblasts was inhibited by 90% and 70%, respectively, after treatment of the cells with a sterol fraction of the *n*-hexane extract ($IC_{50}$ 7.1 units/ml) (*43*). An *n*-hexane fruit extract inhibited androgen binding to cytosolic androgen receptors of rat prostatic tissue in a specific and competitive manner ($IC_{50}$ 330.0–367.5 μg/ml) (*44, 45*). However, in contrast to these findings, the same extract did not inhibit the binding of [$^3$H]dihydrotestosterone to androgen receptors in cultured human foreskin fibroblasts (*46*). Oral administration of an *n*-hexane extract (160 mg/day) inhibited the binding of $^3$H-labelled 17β-estradiol to the nuclear estrogen receptors in samples of prostatic tissue from patients with BPH. Binding to the cytosolic and nuclear estrogen and androgen receptors was measured by saturation analysis and an enzyme-linked immunosorbent assay (*47*).

The effect of an *n*-hexane extract of the fruit was evaluated in two human prostatic cell lines, LNCaP and PC3, which are respectively responsive and unre-

sponsive to androgen stimulation. The extract (100 μg/ml) induced proliferation and differentiation in LNCaP cells, but not in PC3 cells, suggesting that the androgen receptor plays a role in mediating the effects of the fruit in LNCaP cells (*48*). In PC3 cells cotransfected with genes for wild-type androgen receptor and a chloramphenicol acetyltransferase reporter under the control of an androgen-responsive element, the extract (25 μg/ml) inhibited androgen-induced chloramphenicol acetyltransferase transcription by 70% (*48*).

*n*-Hexane, 90% ethanol and supercritical carbon dioxide extracts of the fruit inhibited 5α-reductase activity in vitro (*37, 43, 46, 49–53*). A lipidosterolic extract of the fruit (100 μg/ml) inhibited 5α-reductase activity in the rat ventral prostate by 50%, and reduced conversion of testosterone into dihydrotestosterone in human foreskin fibroblasts by 90%. The conversion of dihydrotestosterone to 5α-androstane-3α-17β-diol by 3α-ketosteroid oxidoreductase was also partially inhibited in cultured human foreskin fibroblasts (*43*). An *n*-hexane extract of the fruit inhibited the activity of both 5α-reductase and 17β-hydroxysteroid dehydrogenase in cultures of epithelial cells ($IC_{50}$ 60 and 40 μg/ml, respectively) and fibroblast cells ($IC_{50}$ 30 and 200 μg/ml, respectively) obtained from the prostates of patients with BPH (*50*). One study reported no effect of several lipidosterolic extracts of the fruit on the activity of 5α-reductase from human prostate or on dihydrotestosterone binding to the rat prostatic androgen receptors at concentrations up to 100 μg/ml (*51*). The reasons for these conflicting results are unclear, and may be due to the different methodologies used. Recently, it has been demonstrated that human 5α-reductase has two isoforms, type 1 and type 2; finasteride, a testosterone 5α-reductase inhibitor has been shown to be a selective inhibitor of the type 2 isoform (inhibitory concentration [$K_i$] 7.3 nmol/l). Furthermore, an *n*-hexane extract of the fruit was a non-competitive inhibitor of the type 1 isoform ($IC_{50}$ 7.2 μg/ml) and an uncompetitive inhibitor of type 2 ($IC_{50}$ 4.9 μg/ml) (*52*). A 90% ethanol extract of the fruit showed a dose-dependent inhibition of 5α-reductase activity in the epithelium (29% inhibition) and stroma (45% inhibition) of prostate tissue from patients with BPH (*52*). When the extract was fractionated into saponifiable, non-saponifiable and hydrophilic subfractions, only the saponifiable subfraction (consisting mainly of lauric, oleic, myristic and palmitic acids) was active. Of these fatty acids, lauric acid was the most active: it inhibited epithelial and stromal 5α-reductase activity by 51% and 42%, respectively. The inhibition by lauric acid was noncompetitive and dose-dependent up to a concentration of 0.2 mmol/l. The nonsaponifiable fraction, consisting mainly of phytosterols, was weakly active, while the hydrophilic subfractions, containing carbohydrates, amino acids and polysaccharides, were inactive (*53*). A supercritical extract of the fruit inhibited 5α-reductase activity in homogenates of cultured human foreskin fibroblasts ($IC_{50}$ 0.025 mg/ml) (*46*).

One study compared testosterone metabolism in primary cultures of epithelial cells and fibroblasts obtained from the prostates of patients with BPH and prostate cancer. In all cultures, androst-4-ene-3,12-dione, formed by the oxidation of testosterone by 17β-hydroxysteroid dehydrogenase, accounted for 80%

of all metabolites recovered. An *n*-hexane extract of the fruit inhibited the formation of androst-4-ene-3,12-dione in both cell types, indicating that it inhibited the activity of 17β-hydroxysteroid dehydrogenase, unlike finasteride, which was inactive (*50*).

An increase in the activity of 3α-hydroxysteroid-oxidoreductase (the enzyme that metabolizes dihydrotestosterone into the inactive androstenediol form) in prostate tissue from patients with BPH was reported following treatment of patients with an *n*-hexane extract of the fruit (320 mg daily for 3 months). Analysis of enzyme kinetics showed that the $V_{max}$ of 3-hydroxysteroid-oxidoreductase was significantly enhanced in the prostate stroma of treated patients. Since 3-hydroxysteroid-oxidoreductase also has a strong substrate affinity for prostaglandins, increased activity of the enzyme may also increase the metabolism of prostaglandins, thereby accounting for the reduction of prostaglandin-mediated congestion or intraprostatic oedema formation (*54*).

Intragastric administration of an *n*-hexane extract of the fruit to castrated rats for 60–90 days inhibited the increase in total weight of the prostate induced by estradiol and testosterone (*55*). Intragastric administration of a 90% ethanol extract to castrated rats (6 ml/kg body weight, weekly for 8 weeks) inhibited the increase in weight of the ventral prostate, seminal vesicles and coagulation glands induced by testosterone (*37*). Intragastric administration of a 90% ethanol extract of the fruit inhibited prostate growth stimulated by both estradiol and dihydrotestosterone in nude mice into which prostate tissue from humans with BPH had been transplanted (*56*). An *n*-hexane extract of the fruit (30 μg/ml) inhibited the proliferation of human prostate cells induced by basic fibroblast growth factor. Lupenone, hexacosanol and an unsaponified fraction of the extract markedly inhibited the proliferation of human prostate cells induced by basic fibroblast growth factor, but had only a minimal effect on basal cell proliferation (*57*).

### Effects on signal transduction

Addition of an *n*-hexane extract of the fruit (1–10 μg/ml) to Chinese hamster ovary cells completely inhibited the effects of prolactin on potassium conductance, protein kinase C activity and intracellular concentrations of calcium. These results suggest that the extract may inhibit prolactin-induced prostatic growth by interfering with the transduction signals involving the prolactin receptor (*58*). Lipidosterolic extracts of the fruit noncompetitively inhibited radioligand binding to human prostatic $\alpha_1$-adrenoceptors and agonist-induced [$^3$H]inositol phosphate formation (*59*).

## *Clinical pharmacology*

### Placebo-controlled clinical trials

Eleven double-blind, placebo-controlled studies have assessed the effects of lipidosterolic extracts of Fructus Serenoae Repentis in the symptomatic treatment of mild to moderate BPH (*26–33, 60–62*). The number of patients in each study

ranged from 22 to 205, and the dosage of the extract was generally 160 mg twice daily for 1–3 months. All but one study (*61*) reported that the extract was significantly more effective than placebo in reducing the symptoms of mild to moderate BPH. In this study of 70 patients, which was also randomized, although a significant improvement in flow rate was seen in patients treated with either a hexane extract of the fruit (320 mg) or placebo daily for 3 months, no significant difference between the treatment groups was observed (*61*). However, most studies demonstrated an increase in urinary flow rate and a decrease in postvoid residual urine volume (*26*). In another study which was also randomized, 205 patients were treated with 320 mg extract or placebo daily for 3 months. The study concluded that the extract was superior to placebo in reducing the total symptom score (polyuria, nocturia, dysuria, and urgency and hesitancy of micturition), improving the quality of life score, and increasing urinary volume (*62*).

A study was performed on 176 patients with BPH who had been unresponsive to placebo treatment in previous clinical studies. After 30 days of treatment with an extract of the fruit (160 mg, twice daily), there was a significant reduction in dysuria, polyuria and nocturia in the treated group as compared with the placebo group. Patients treated with the extract had a significantly greater increase in mean peak urinary flow rate (28.9%), as compared with those that received the placebo (8.5%), and the overall efficacy of the extract was rated higher than that of the placebo by both patients and physicians (*33*).

Another double-blind, placebo-controlled study assessed the effect of a lipidosterolic extract in the reduction of prostate oedema and congestion in 18 patients with BPH. Histopathological analysis of enucleated prostate tissue from patients treated preoperatively with the extract (320 mg daily for 12 weeks) showed a significant decrease in prostate stromal oedema and congestion in treated patients, as compared with those in the placebo group ($P \leqslant 0.05$) (*63*).

### Controlled clinical trials

In a controlled clinical trial, 25 men with symptoms of urinary obstruction were randomized into two groups: 15 patients received no treatment, while 10 were treated with an *n*-hexane extract of Fructus Serenoae Repentis (320 mg extract daily). After 3 months, prostatic specimens were removed by suprapubic prostatectomy and were sectioned into three regions (i.e. periurethral, subcapsular and intermediate). In each region, the concentration of testosterone, dihydrotestosterone and epidermal growth factor was measured by radioimmunoassay. In the patients treated with the extract, a significant reduction ($P < 0.001$) in the concentration of dihydrotestosterone (50%) and epidermal growth factor (50%), and a significant increase ($P < 0.001$) in testosterone levels (125%), were observed in the periurethral region (*64*).

## *Clinical trials without controls*

Numerous clinical studies without controls of men with BPH have reported improvements in both objective and subjective variables after treatment with lipidosterolic extracts of the fruit (*15–28*). The largest trial of 1334 patients treated with 320 mg of a lipidosterolic fruit extract daily for 6 months showed an improvement in postvoid residual urine volume (50% decrease), nocturia (54% decrease) and polyuria (37% decrease) (*16*). The results of a prospective multicentre study in which 435 patients with BPH were treated with a lipidosterolic extract of the fruit (320 mg daily for 3 years) showed a steady improvement in micturition. The improvement was due to a marked decrease in symptoms and postvoid residual urine volume (50% decrease), and an increase in peak urinary flow rate (about 25%) (*17*). Another multicentre study analysed the effect of a lipidosterolic extract of the fruit (160 mg twice daily for 3 months) in 305 patients with mild to moderate BPH. After treatment, increases in maximal and mean urinary flow rates (of 25% and 27%, respectively) and a 35% improvement in the mean International Prostate Symptom Score were seen (*18*). Other studies have also reported improvements in symptoms and objective measurements of disease severity after 1–6 months of treatment with a lipidosterolic extract of the fruit (320 mg daily) (*19–28*). Generally, studies involving periodic evaluation over the course of treatment have demonstrated that improvements in both objective and subjective variables were progressive over time (*17*, *24–27*).

### Comparative trials

An *n*-hexane extract of Fructus Serenoae Repentis, finasteride and $\alpha_1$-receptor antagonists have been shown to be clinically effective in the treatment of BPH in comparative trials (*16*, *65–69*). One large international randomized, double-blind clinical trial compared the efficacy of the extract (320 mg daily) with that of finasteride (5 mg daily) in the treatment of 1098 patients with mild to moderate BPH. After 6 months of therapy, the International Prostate Symptom Score decreased from baseline by 37% in patients treated with the extract as compared with a decrease of 39% in patients who received finasteride. No significant difference was observed between the treatment groups in improvement of patient-rated quality of life scores and the primary end-point of objective symptom score. Both treatments resulted in improved peak urinary flow rates and a reduction in the size of the prostate. Peak urinary flow rate increased from 10.6 ml/s to 13.3 ml/s in patients treated with the extract, and from 10.8 ml/s to 14.0 ml/s in those who received finasteride. The size of the prostate was reduced by 6% in patients treated with the extract, and by 18% in those treated with finasteride. Serum prostate-specific antigen levels were reduced by 41% following finasteride treatment, but remained unchanged in patients treated with the extract (*16*).

Other smaller, shorter, randomized double-blind trials involving groups of 41–63 patients compared the efficacy of the fruit extract (320 mg daily) with the $\alpha_1$-receptor antagonists alfuzosin and prazosin (*68, 69*). In a 3-week comparative trial with alfuzosin, the total mean symptom score using Boyarsky's rating scale improved by 27% and 39% in patients treated with the extract and alfuzosin, respectively. Although improvements in the peak urinary flow rates were greater in the alfuzosin-treated group, there was no significant difference between the treatments (*68*). In a 12-week randomized trial comparing the efficacy of a fruit extract (in 20 patients) and prazocin (in 21 patients), improvements in polyuria, mean urinary flow rate and postvoid residual urine volume were similar in both groups, but no statistical analysis of the data was provided by the investigators (*67*). Further large, well-designed, randomized trials of long duration are necessary to compare adequately the clinical efficacy of Fructus Serenoae Repentis and $\alpha_1$-receptor antagonists.

Four reviews of the randomized controlled clinical trials have indicated that lipidosterolic extracts of the fruit improve the symptoms of urinary tract disorders and urinary flow rates in men with mild to moderate BPH (*14, 68–70*).

### Pharmacokinetics

The pharmacokinetics of Fructus Serenoae Repentis were investigated in a bioequivalence study that compared a new capsule formulation (320 mg/capsule) to a reference preparation (160 mg/capsule). Concentrations of the components of the extract were measured in plasma samples from 12 healthy fasting males (mean age 24 years) after oral administration of 320 mg extract (either one capsule of 320 mg or two capsules of 160 mg) (*71*). However, the methodology used in this study was questionable.

Tissue distribution was measured in rats after intragastric administration of a lipidosterolic extract supplemented with radiolabelled oleic acid, lauric acid or β-sitosterol. This investigation demonstrated that the uptake of the extract was much higher in the prostate than either the liver or genitourinary tissues (*72*).

### Toxicity

Clinical studies have shown that extracts of Fructus Serenoae Repentis are very well tolerated in humans (*16, 69*). Minor gastrointestinal side-effects have been reported in most of the clinical trials, but results from standard blood chemistry tests were normal (*69*).

## Contraindications

Owing to its effects on androgen and estrogen metabolism, the use of Fructus Serenoae Repentis during pregnancy or lactation and in children under the age of 12 years is contraindicated.

## Warnings

Fructus Serenoae Repentis relieves the symptoms associated with BPH, but does not have an effect on the size of the prostate. If symptoms worsen or do not improve, or in cases of blood in the urine or acute urinary retention, contact a physician (*1*).

## Precautions

### *Pregnancy: teratogenic effects*

See Contraindications. There is no therapeutic rationale for the use of Fructus Serenoae Repentis during pregnancy.

### *Pregnancy: non-teratogenic effects*

See Contraindications. There is no therapeutic rationale for the use of Fructus Serenoae Repentis during pregnancy.

### *Nursing mothers*

See Contraindications. There is no therapeutic rationale for the use of Fructus Serenoae Repentis during lactation.

### *Paediatric use*

See Contraindications.

### *Other precautions*

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; or carcinogenesis, mutagenesis and impairment of fertility.

## Adverse reactions

Both short- and long-term clinical studies have found that extracts of Fructus Serenoae Repentis are very well tolerated. Occasional nausea, diarrhoea and other minor gastrointestinal complaints have been reported (*18*).

## Dosage forms

Crude drug, lipidosterolic extracts (*n*-hexane, 90% ethanol or fluid [carbon dioxide] supercritical extracts standardized to contain 70–95% free fatty acids and corresponding ethyl esters), and preparations thereof. Store in a tightly closed container in a cool, dry place.

## Posology

(Unless otherwise indicated)
Daily dosage: 1–2 g crude drug or 320 mg (as a single dose or 160 mg twice daily) of a lipidosterolic extract (*n*-hexane, 90% ethanol or supercritical

fluid [carbon dioxide] extract standardized to contain between 70 and 95% free fatty acids and corresponding ethyl esters) or equivalent preparations (*16–33, 60–62*).

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# Fructus Silybi Mariae

## Definition

Fructus Silybi Mariae consists of the dried ripe fruits, freed from the pappus, of *Silybum marianum* (L.) Gaertn., Asteraceae (*1*, *2*).

## Synonyms

*Carduus marianus* L., *Carthamus maculatum* Lam., *Cirsium maculatum* Scop., *Mariana mariana* (L) Hill., *Silybum maculatum* Moench. (*3*, *4*). Asteraceae are also known as Compositae.

## Selected vernacular names

Akùb, Artichnuat sauvage, blessed thistle, bull thistle, cardo blanco, cardo de burro, cardo mariano, carduo mariano, chardon argente, chardon-marie, épine blanche, Frauendistelfrüchte, fructus cardui mariae, fruit de chardon marie, holy thistle, kharshat barri, khorfeish, kocakavkas, kuub, Lady's milk, Lady's thistle, lait de Notre Dame, marian thistle, máriatövis-termés, mariazami, Mariendistel, Mariendistelfrüchte, Marienkörner, maritighal, mild marian thistle, milk thistle, pternix, shawkeddiman, Silberdistil, silybe, silybon, silybum, St Mary's thistle, thistle, thistle of the Blessed Virgin, true thistle, variegated marian thistle (*3–7*).

## Geographical distribution

Indigenous to North Africa, Asia Minor, southern Europe and southern Russian Federation; naturalized in North and South America, Australia, China and Central Europe (*3*, *4*).

## Description

An annual or biennial herb, stem 20–150 cm high, green, glabrous or slightly arachnoid-pubescent. Leaves alternate, large, glossy green, white-veined or variegated, glabrous with strongly spiny margins, basal leaves (25–50 cm long, 12–25 cm wide) cauline, pinnatifid. Inflorescence large, composed of red-purple, hermaphrodite, tubular florets gathered into a capitulum (2.5–4.0 cm in diameter), tucked in an involucre with thorny external bracts. Fruits 6–7 mm long, composed of 6–8 hard-skinned achenes with a white, silky pappus (15–20 mm in diameter) at apex. $2n = 34$ (*3*, *7–12*).

## Plant material of interest: dried ripe fruits, freed from the pappus

### *General appearance*

Obliquely obovoid with remainder of a flower crown on its top; 6–7 mm long, up to 3 mm wide, 1.5 mm thick. Testa shiny brownish-black or matt greyish-brown, with dark or greyish-white dots. At the tip, there is a projecting yellowish cartilaginous, swollen ring, and at the bottom at the side, a canaliculate hilum. Silvery pappus absent from the drug. Varieties are white, grey and black (*2, 4*).

### *Organoleptic properties*

Odour: scarcely perceptible; taste: oily, bitter (*2–4*).

### *Microscopic characteristics*

Pericarp epidermis a colourless palisade layer of cells (about 75 µm long and 8 µm wide) with a strongly thickened outside wall, which reduces the lumen in that part of the cell to a slit; subepidermal layer composed of colourless, thin-walled, parenchyma cells or groups of parenchyma cells alternating with a variable number of pigmented cells; innermost layer mostly collapsed and containing cigar-shaped or monoclinic prismatic crystals of calcium oxalate. Testa epidermis consists of large, lemon-yellow, palisade-like, elongated cells (about 150 µm long) with striated walls and narrow lumen widening slightly at the ends; subepidermal layers have lignified and pitted cells (*2, 4*).

### *Powdered plant material*

Brownish-yellow. Fragments of colourless palisade-like epidermal cells from the fruit wall with attached pigment layer; epidermal cells about 75 µm long and 8 µm wide; cigar-shaped or monoclinic prismatic crystals of calcium oxalate; fragments of lemon-yellow, palisade-like testa cells about 150 µm long; fragments of embryo with thin-walled cells, small druses and lipophilic substances (*2*).

## General identity tests

Macroscopic and microscopic examinations (*2, 4*), and thin-layer chromatography for the presence of marker compounds (taxifolin, silybin, silydianin and silychristin) (*2, 13*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

### *Foreign organic matter*
Not more than 2% (*1*, *2*).

### *Total ash*
Not more than 8% (*1*, *2*).

### *Acid-insoluble ash*
Not more than 1% (*1*).

### *Water-soluble extractive*
Not less than 10% (*1*).

### *Loss on drying*
Not more than 8% (*2*).

### *Pesticide residues*
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

### *Heavy metals*
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

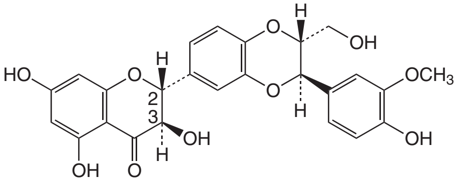
### *Radioactive residues*
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

### *Other purity tests*
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

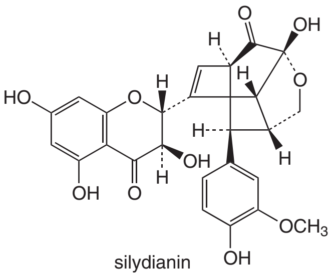
## Chemical assays
Contains not less than 1.5% silymarin, calculated as silybin, as analysed by high-performance liquid chromatography (*2*). Other high-performance liquid chromatography methods are also available (*3*, *17*, *18*).

## Major chemical constituents
The major active constituents are flavonolignans (1.5–3.0%), collectively known as silymarin. The major components of the silymarin complex are the four

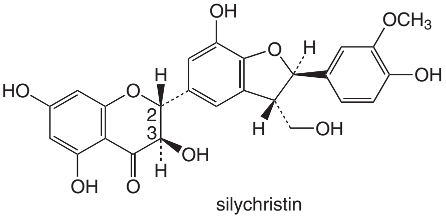
isomers silybin and isosilybin (a 1 : 1 mixture of diastereoisomers), silychristin and silydianin. Other flavonolignans identified include 2,3-dehydrosilybin and 2,3-dehydrosilychristin. Taxifolin, a 2,3-dihydroflavonol, which may be regarded as the parent flavonol of the silymarin compounds, is another major marker for Fructus Silybi Mariae (*3, 4, 6–8, 19, 20*). The structures of the major silymarin components and taxifolin are presented below.



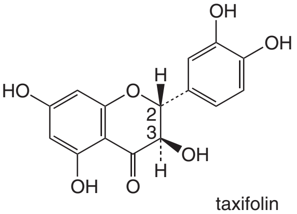
silybin



silydianin



silychristin



taxifolin

## Medicinal uses

### *Uses supported by clinical data*

Supportive treatment of acute or chronic hepatitis and cirrhosis induced by alcohol, drugs or toxins (*21–34*).

### *Uses described in pharmacopoeias and in traditional systems of medicine*

Treatment of dyspeptic complaints and gallstones (*7, 35*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of amenorrhoea, constipation, diabetes, hay fever, uterine haemorrhages and varicose veins (*6*).

## Pharmacology

Most of the biochemical and pharmacological studies have been performed using a standardized silymarin preparation, or its major constituent, silybin.

## Experimental pharmacology

### Antioxidant activity

Silymarin and silybin have antioxidant activity in vitro: both react with oxygen-free radicals such as hydroxyl anions, phenoxy radicals and hypochlorous acid in various model systems such as human platelets, human fibroblasts, rat liver microsomes and mitochondria, and using enzymatically and non-enzymatically generated free inorganic radicals (*36–42*). The production of superoxide anion radicals and nitric oxide was inhibited after treatment of isolated rat Kupffer cells with silybin ($IC_{50}$ 80 μmol/l) (*43*). Both silymarin and silybin inhibited free radical-induced lipid peroxidation in microsomal and mitochondrial preparations of human red blood cells, thereby stabilizing the structure of the cell membrane (*36, 44–52*). Inhibition of cyclic AMP-dependent phosphodiesterase by silybin, silydianin and silychristin has been demonstrated in vitro. Since cyclic AMP is known to stabilize lysosomal membranes, an increase in the concentration of this nucleoside has been proposed to be the mechanism of membrane stabilization and thus the anti-inflammatory activity of silymarin (*53*). Silybin also inhibits phospholipid synthesis and breakdown in rat liver membranes in vitro, and corrects the alteration in phospholipid metabolism in ethanol-treated rats (*54*). Both silymarin and silybin are incorporated into the hydrophobic–hydrophilic interface of the rat microsomal membrane bilayer and alter the structure by influencing the packing of the acyl chains (*47*).

### Antihepatotoxic activity

Silymarin and silybin inhibited hepatotoxicity induced by paracetamol (acetaminophen), amitriptyline, carbon tetrachloride, ethanol, erythromycin estolate, galactosamine, nortriptyline and *tert*-butyl hydroperoxide in rat hepatocytes in vitro (*55–58*). Silybin reduced ischaemic damage to nonparenchymal hepatic cells and improved post-ischaemic function in pig livers (*59*). Allyl alcohol-induced toxicity, and associated lipid peroxidation and glutathione depletion were suppressed after treatment of isolated rat hepatocytes with silymarin and silybin at concentrations of 0.1 and 1.0 mmol/l, respectively (*60*).

Silybin stimulated macromolecular biosynthesis in vitro and in vivo (*61–64*). Silybin increased the rate of ribosomal RNA synthesis by 20% in rat liver, cultured hepatocytes and isolated liver nuclei, via activation of DNA-dependent RNA polymerase I (*63*). Silybin binds to the regulatory subunit of DNA-dependent RNA polymerase I at the estrogen binding site, thereby acting as a natural steroid effector, and thus activating the enzyme and increasing the rate of ribosomal RNA synthesis (*64*). Silybin had no effect on the transcription of RNA polymerase II or III. The increase of ribosomal RNA synthesis in the liver stimulates the formation of mature ribosomes, and hence protein biosynthesis (*63*). Furthermore, an increase in DNA synthesis was observed in livers from hepatectomized rats treated with silybin (27 mg/kg body weight) (*65*).

Intraperitoneal or intragastric administration of silymarin (15–800 mg/kg body weight) to dogs, mice and rats prevented carbon tetrachloride-induced liver damage (*46*, *66–68*). This effect of silymarin was attributed to its antioxidant activity, a decrease in the metabolic activation of carbon tetrachloride, and stabilization of hepatocyte membranes (*46*, *66*, *67*, *69*). Intragastric administration of silymarin (50 mg/kg body weight) improved the metabolism and tissue distribution of aspirin in rats with carbon tetrachloride-induced liver toxicity (*70*). Intraperitoneal administration of either silymarin or silybin markedly inhibited liver damage induced by paracetamol (acetaminophen), *Amanita phalloides* toxins (e.g. phalloidin and α-amanitin), ethanol, galactosamine, halothane, polycyclic aromatic hydrocarbons, rare earth metals (e.g. cerium, praseodymium and lanthanum) and thallium in various rodent models (*50*, *71–81*). Furthermore, intravenous administration of silybin hemisuccinate sodium salt (50 mg/kg body weight) to dogs given sublethal doses of *Amanita phalloides* (85 mg/kg body weight) prevented the increase in concentration of liver enzymes in the blood and the decrease in clotting factors (*82*). The uptake of [$^3$H]dimethyl phalloidin in isolated rat hepatocytes was inhibited by 79% in cells treated with silybin ester (100 μg/ml) (*73*). However, intravenous administration of silybin (50 mg/kg body weight) to rats inhibited the protective effect of ethanol on paracetamol-induced hepatotoxicity. The combination of ethanol and silybin appeared to lead to inhibition of paracetamol metabolism by microsomes (*83*). Intravenous administration of silybin hemisuccinate sodium salt (50 mg/kg body weight) to mice preinfected with sublethal doses of frog virus 3 attenuated histological changes in hepatocyte nuclei; animals treated with a lethal dose of frog virus 3 showed increased survival times (*84–86*).

Intragastric administration of silymarin (50 mg/kg body weight) to rats inhibited collagen accumulation in early and advanced biliary fibrosis secondary to complete bile duct occlusion induced by sodium amidotrizoate (*87*). Silymarin increased the redox state and the total glutathione content in the liver, intestine and stomach of rats after intraperitoneal administration (200 mg/kg body weight) (*42*, *88*).

In a transplantation experiment, explanted pig liver was subjected to cold-induced ischaemia by storage of the liver at 4 °C for 24 hours, followed by extracorporeal reperfusion for 4 hours. Intravenous administration of 500 mg silybin ester prior to removal of the liver, followed by 400 mg/l during cold storage and 100 mg/h during reperfusion, reduced histological damage to the liver cells (measured by bile production) and improved liver function during reperfusion by 24–66% (measured by bile acid excretion) (*59*).

### Anti-inflammatory and anti-allergic activity

Silybin inhibited neutrophil-mediated histamine release induced by *f*-met peptide and anti-IgE from human basophil leukocytes. The inhibitory effect was significantly attenuated ($P < 0.05$) by elevating the extracellular calcium concentration. However, no effect was observed on histamine release induced by the calcium ionophore A23187 (*89*). Silymarin inhibited neutrophil-

mediated histamine release activated by *N*-formylmethionyl-leucyl-phenylalanine from rat peritoneal mast cells at a concentration of 25 µg/ml (*90*). Silybin inhibited the synthesis of leukotriene $B_4$ ($IC_{50}$ 15 µmol/l) in isolated rat Kupffer cells, but had no effect on prostaglandin $E_2$ formation at concentrations up to 100 µmol/l (*43*). Silymarin, silybin, silydianin and silychristin inhibited the activity of lipoxygenase and prostaglandin synthetase in vitro (*91–93*). The anti-inflammatory activity of silybin was assessed in human polymorphonuclear leukocytes in vitro. The chemotactic and phagocytic activities of the polymorphonuclear leukocytes were not modified by silybin at concentrations of 0.5–25.0 µg/ml. However, the compound did inhibit luminol-enhanced chemiluminescence, suggesting that the mechanism of anti-inflammatory activity involved the inhibition of hydrogen peroxide formation (*94*). Intragastric administration of silymarin reduced carrageenan-induced footpad oedema in rats ($ED_{50}$ 62.42 mg/kg body weight). Topical application of silymarin inhibited xylene-induced ear inflammation in mice, and its activity was similar to that of indometacin (25 mg/kg body weight). In addition, silymarin inhibited leukocyte accumulation in inflammatory exudates following intraperitoneal administration of carrageenan to mice (*95*).

Intragastric administration (25–1000 mg/kg body weight) of an acetone extract of the fruit containing silybin increased the volume and dry mass of excreted bile in rats (*96*). Intragastric administration of silymarin (100 mg/kg body weight) prevented gastric ulceration in rats induced by cold-restraint and pyloric ligation, but was not effective against ethanol-induced ulcers (*97*). Intragastric administration of silymarin (100 mg/kg body weight) to rats prevented gastric injury induced by ischaemia-reperfusion (*98*).

## Clinical pharmacology

### Alcohol-induced hepatitis

The efficacy of a standardized silymarin preparation for the treatment of alcohol-induced cirrhosis was assessed in six placebo-controlled clinical trials (*24–27*, *31*, *33*, *99*). The majority of these studies involved between 50 and 100 patients, with one study including 170 patients (*26*). Patients generally received an oral dose of 280–420 mg (140 mg two or three times daily) of a standardized silymarin preparation or placebo. One of the studies had a treatment period of up to 4 years, and used survival rates as their outcome parameter. The results of this study showed a significant decrease in the mortality of patients treated with silymarin as compared with placebo ($P < 0.05$) (*26*). After treatment with the silymarin preparation (140 mg twice daily), a decrease in total bilirubin, liver enzymes and serum N-terminal propeptide of collagen type III levels was observed (*25*). A 6-month trial that was also double-blind assessed the efficacy of silymarin in patients who had histological documentation of chronic alcoholic hepatitis. Silymarin treatment improved histology, and lymphocyte proliferation and lipid peroxidation (*24*). In two studies that were also randomized and double-blind, treatment of 163 patients with the

silymarin preparation decreased serum levels of liver enzymes, improved liver function, and returned sulfobromophthalein levels to normal, as compared with placebo (*27, 31*). Another trial that was also randomized and double-blind analysed the effects of silymarin in 116 patients with alcohol-induced hepatitis, 58 of whom had liver cirrhosis. Patients received 420 mg silymarin or placebo daily for 3 months. A significant improvement was noted in both groups ($P < 0.05$); however, silymarin was not more effective than placebo (*99*).

Five double-blind clinical trials assessed the efficacy of silymarin in the treatment of various chronic liver diseases induced by alcohol (*22, 23, 25, 29, 30*). In four of these trials, treatment of patients with 420 mg of the silymarin preparation daily for 6 months decreased the serum levels of bilirubin, procollagen III peptide and liver enzymes, and increased serum glutathione peroxidase activity and lectin-induced lymphoblast transformation (*23, 25, 29, 30*). In the fifth study, which was also placebo-controlled, the efficacy of silymarin was assessed in 20 patients with various chronic liver diseases. After 13 months of treatment (420 mg daily), histopathological findings showed improvements in the treated group as compared with the group that received placebo (*22*).

In a randomized trial of 60 patients with diabetes caused by alcohol-induced cirrhosis, patients received either 600 mg silymarin daily or no treatment for 6 months (*100*). The blood glucose and malondialdehyde levels, daily insulin need and fasting insulinaemia levels were all significantly lower in treated patients than in those that were untreated ($P < 0.05$), and lower than initial baseline values (*100, 101*). A study without controls assessed the efficacy of a standardized silymarin preparation (420 mg daily) in inhibiting fibrotic activity in 277 patients with various chronic liver diseases. In liver fibrosis, the serum level of the procollagen III peptide increases. The elevated levels of this peptide decreased over the 4-week treatment period (*102*). In a drug monitoring study without controls, 108 patients with alcohol-induced hepatotoxicity and liver inflammation were treated with silymarin (200–400 mg/kg body weight, in a single dose) daily for 5 weeks. After treatment, the serum procollagen III peptide and liver enzyme levels were lower in comparison to the initial baseline values. The preparation was generally well tolerated in 98% of patients (*103*). The safety and efficacy of silymarin were evaluated in over 3500 patients in two drug-monitoring studies. In one study, 2637 patients with various liver disorders were treated with a standardized silymarin preparation (560 mg, given in four divided doses) daily for 8 weeks. Subjective symptoms decreased by 63%, clinical findings improved and elevated serum levels of liver enzymes were reduced in the treated group. Treatment was rated as very good, good or satisfactory by 88% of the physicians (*21*). Minor gastrointestinal side-effects were reported in 1% of patients (*21, 28*).

### Acute and chronic viral hepatitis

Three controlled trials assessed the efficacy of silymarin in the treatment of acute viral hepatitis (*104–106*). In a randomized, double-blind study of 57

patients with acute viral hepatitis A or B, patients received 420 mg of a standardized silymarin preparation or placebo daily for 3 weeks. In the treatment group, 40% of patients had a normalized blood bilirubin level, as compared with 11% of the placebo group; 82% of the treated patients had a normalized blood level of aspartamine transaminase, as compared with 52% of the placebo group. There was no difference between the two groups in the number of patients who developed immunity (*105*). In another trial, the duration of inpatient care was shown to be shorter for patients treated with silymarin, compared to those who received supportive care (23.3 and 30.4 days, respectively). In patients with viral hepatitis B, treatment with silymarin led to a shorter interval to the development of immunity (30.4 days), compared to supportive therapy only (41.2 days) (*104*). A double-blind study in patients with acute viral hepatitis indicated that daily treatment with 420 mg silymarin (three doses of 140 mg) decreased the complications associated with the infection (*106*).

A 12-month study combining two double-blind, placebo-controlled trials assessed the efficacy of silymarin in the treatment of chronic hepatitis, with or without cirrhosis, in 36 patients. Patients were treated with 420 mg of a standardized silymarin preparation or placebo daily for 3–12 months. Assessment of serum levels of bilirubin and liver enzymes did not reveal any significant differences in liver function between the treatment and placebo groups. However, histological improvements were noted in patients who received silymarin (*107*).

### Organic compound-induced hepatitis

A controlled clinical study of patients with a 5–20-year history of occupational exposure to toluene and/or xylene vapours was performed to assess the efficacy of a standardized silymarin preparation on liver function. Thirty patients were treated orally with 140 mg of the preparation three times daily for 30 days, and the results were compared with those from 19 untreated matched controls. Both liver function and platelet counts markedly improved in the treated patients (the elevated serum levels of glutamic oxaloacetic transaminase and glutamic pyruvic transaminase were reduced, and the low platelet numbers increased) as compared with the controls (*32*). In another study, the effects of a silymarin preparation (420 mg/day) on liver function in 14 patients chronically exposed to the organophosphate malathion were assessed. After treatment, patients showed no improvement in liver function tests when compared with the controls (10 healthy volunteers) (*108*).

### Drug-induced hepatitis

A double-blind, placebo-controlled study assessed the efficacy of silymarin in the prevention of hepatic damage induced by psychotropic drugs. Sixty patients receiving chronic therapy with psychotropic drugs (butyrophenones or phenothiazines) were treated orally with 800 mg silymarin or placebo daily for 90 days. Silymarin treatment improved liver function and reduced lipoperoxida-

tive hepatic damage as determined by serum malondialdehyde levels (the end-product of the oxidation of polyunsaturated fatty acids) (*109*). A small clinical study found improvements in biochemical parameters in 19 patients using psychotropic drugs after 6 months of treatment with silymarin (*110*).

## Toxin-induced hepatitis

Numerous case reports have indicated that silymarin and silybin are effective in the treatment of poisoning due to ingestion of the deathcap mushroom *Amanita phalloides* (*34, 111–114*). *Amanita* toxins inhibit the activity of RNA polymerase in hepatocytes, causing cell death after 12–24 hours. In a clinical trial without controls, 60 patients were treated intravenously with silybin (20 mg/kg body weight, daily for 1–2 days), 24–36 hours after ingestion of *Amanita phalloides*. The survival rate was 100% (*34*). Results of a multicentre study of 252 cases of poisoning due to ingestion of *Amanita phalloides* indicated that intravenous infusion of silybin (20 mg/kg body weight, daily for 1–2 days), in combination with the standard management techniques, dramatically reduced mortality, without producing side-effects (*111–113*).

Assessment of the clinical trials of silymarin for the treatment of hepatitis induced by alcohol, drugs or toxins, and acute and chronic viral hepatitis should be interpreted with caution because of the small number of patients involved, the heterogeneity of diagnoses and outcome parameters, and the inconsistent reporting of alcohol intake by patients during the studies (*115*).

## Pharmacokinetics

In a randomized, four-way crossover study without controls, a single dose of 102, 153, 203 or 254 mg silybin was administered orally to six healthy males. Silybin and isosilybin concentrations in plasma were measured as unconjugated compounds as well as total isomers after hydrolysis using high-performance liquid chromatography. Areas under the curve were linear with the dose, and only 10% of total silybin in the plasma was in the conjugated form. The elimination half-life of unconjugated silybin was less than 1 hour; that of total silybin was estimated to be 6 hours. Approximately 5% of the dose was excreted into the urine as total silybin, corresponding to a renal clearance rate of 30 ml/min (*116*).

After oral administration of a single dose of 560 mg silymarin (equivalent to 240 mg silybin) to six healthy volunteers, maximum serum concentrations of silybin were low, ranging from 0.18 to 0.62 μg/ml. Only 1–2% of the dose was excreted in the urine during the 24 hours following administration. After oral administration of a single dose of 140 mg silymarin (equivalent to 60 mg silybin) to 14 patients who had undergone cholecystectomy, bile collected from the T-tube drains contained 11–47 μg/ml silybin, equivalent to 7–15% of the dose, after 24 hours (*117*).

Following oral administration of a single dose of a standardized silymarin preparation (140 mg) to nine patients who had undergone cholecystectomy, the urinary and biliary excretion of silybin, silydianin and silychristin were mea-

sured. The urinary excretion of silybin and silychristin was insignificant. Both silybin and silychristin were excreted in the bile in the form of sulfate and glucuronide conjugates. The total elimination of silybin was estimated to be 20–40% and that of silychristin was 4–10%. Urinary excretion of silymarin occurred over a 24-hour period, with maximum excretion occurring between 2 and 9 hours after administration (*118*).

The bioavailability of silymarin varies considerably and is dependent on the formulation of the product (*119*).

## Contraindications

Fructus Silybi Mariae is contraindicated in cases of known allergy to plants of the Asteraceae family (*120*).

## Warnings

No information available.

## Precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Fructus Silybi Mariae should not be administered during pregnancy or lactation or to children without medical supervision.

## Adverse reactions

Crude drug: one case of anaphylactic shock was reported in a patient ingesting a tea prepared from Fructus Silybi Mariae (*120*). Standardized preparation: a mild laxative effect has been reported (*35*).

## Dosage forms

Usually standardized extracts for phytomedicine; crude drug for decoction (*4*). Store in a well-closed container, protected from light and humidity (*2*).

## Posology

(Unless otherwise indicated)
Daily dosage: 12–15 g crude drug (*35*); 200–400 mg silymarin, calculated as silybin, in standardized preparations (*35*).

A parenteral preparation, silybin hemisuccinate sodium salt, is available in Germany for treatment of poisoning due to ingestion of *Amanita phalloides* (*111–114*, *121*). The total dosage is 20 mg/kg body weight, given as four infusions over a 24-hour period, with each dose administered over a 2-hour period (*121*).

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# Herba Tanaceti Parthenii

## Definition

Herba Tanaceti Parthenii consists of the dried leaves (*1*), or dried aerial parts of *Tanacetum parthenium* (L.) Schultz Bip. (Asteraceae) (*2*, *3*).

## Synonyms

*Chrysanthemum parthenium* (L.) Bernh., *Leucanthemum parthenium* (L.) Gren & Gordon, *Matricaria eximia* Hort., *M. parthenium* L., *Pyrethrum parthenium* (L.) Sm. (*4–6*). Asteraceae are also known as Compositae.

## Selected vernacular names

Acetilla, âghovân, alfinetes de senhora, altamisa, altamisa mexicana, altamza, amargosa, artemijio, artemijo, artmija, bachelor's buttons, boulet, bouton d'argent, camamieri, camomilla, camoumida, camsumilha, canamelha, featherfew, featherfoil, feather-fully, febrifuge plant, feverfew, feverfew tansy, flirtwort, grande camomille, hierba Santa Maria, manzanilla, matricaria, matricaria comum, midsummer daisy, Moederkruid, Mutterkraut, natsushirogiku, Santa Maria, varadika, vettervoo (*3–5*, *7*).

## Geographical distribution

Indigenous to south-east Europe, as far east as the Caucasus, but commonly found throughout Europe and the United States of America (*8*, *9*).

## Description

A perennial plant up to 30–90 cm high. Stem up to 5 mm in diameter, more or less branched. Leaves greenish-yellow, 2–5 cm, sometimes up to 10 cm, long; pinnatisect to bipinnate, petiolate, alternate, more or less pubescent on both sides. Capitula grouped in wide corymbs of 5–30 florets, each floret with long pedicels, and 1.2–2.2 cm in diameter. Involucre in the shape of a hemisphere, 6–8 mm wide and composed of numerous partly overlapping sheathing bracts; interior bracts narrow, obtuse, scarious and fragmented at apex; exterior bracts oval and membranous on edges. Central hermaphrodite flowers yellow, tubiform, 5-toothed, and have 5 stamens inserted on the corolla; filaments entirely free, but the anthers welded together in a tube, through which passes the style

with its 2 stigmatic branches. Peripheral female flowers have a white 3-toothed ligule 2–7 mm long. Fruit an achene, 1.2–1.5 mm long, brown when mature, with 5–10 white longitudinal ribs; glandular with a short membranous, crenulate crown (*3*, *5*, *7*, *10*).

## Plant material of interest: dried leaves or aerial parts

### General appearance

Stem bright green, longitudinally furrowed, almost quadrangular, slightly pubescent. Leaves pinnatisect or bipinnate, divided into 5–9 segments of which the lamina is coarsely crenate at edge, apex obtuse, a prominent central vein to the underside, both surfaces pubescent (*1–3*).

### Organoleptic properties

Odour: camphorous; taste: bitter (*3*).

### Microscopic characteristics

Epidermal cells have sinuate walls, striated cuticle and anomocytic stomata, more frequent on the lower epidermis. Trichomes, more abundant on the lower epidermis, of 2 types: covering trichomes uniseriate, consisting of a trapezoidal basal cell with a striated cuticle composed of 3–5 small, rectangular, thick-walled cells, and elongated, tapering apical cells, often curved at 90° to the axis of the basal cell; glandular trichomes slightly sunken, composed of a short, biseriate, 2- or 4-celled stalk and a biseriate head of 4 cells, around which the cuticle forms a bladder-like covering; spherical, echinulate pollen grains about 25 µm in diameter with 3 germinal pores (*1*, *3*).

### Powdered plant material

Epidermal cells have sinuate walls and a striated cuticle. Numerous large multicellular, uniseriate trichomes, consisting of a trapezoidal basal cell with a striated cuticle composed of 3–5 small, rectangular, thick-walled cells, and terminated by elongated, tapering apical cells, often curved at 90° to the axis of the basal cell. Secretory hairs sparse, but typical of Asteraceae family. Numerous punctate spiral vessels; stratified parenchyma or collenchyma cells; isolated calcium oxalate crystals in the interior of the mesophyll (*3*).

## General identity tests

Macroscopic and microscopic examinations, thin-layer chromatography, and high-performance liquid chromatography for the presence of parthenolide (*1*, *3*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*11*).

### *Foreign organic matter*

Not more than 10%, including stems greater than 5 mm in diameter (*1*, *3*).

### *Total ash*

Not more than 12% (*1*, *3*).

### *Acid-insoluble ash*

Not more than 3% (*1*, *2*).

### *Water-soluble extractive*

Not less than 15% (*2*).

### *Loss on drying*

Not more than 10% (*1*, *3*).

### *Pesticide residues*

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*12*). For other pesticides, see the *European pharmacopoeia* (*12*), and the WHO guidelines on quality control methods for medicinal plants (*11*) and pesticide residues (*13*).

### *Heavy metals*

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*11*).

### *Radioactive residues*

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*11*) for the analysis of radioactive isotopes.

### *Other purity tests*

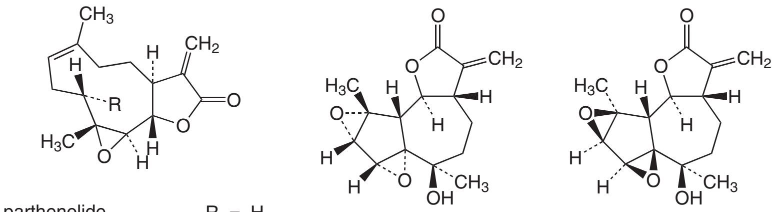
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

## Chemical assays

Contains not less than 0.2% parthenolide (dry weight), as determined by high-performance liquid chromatography (*3*).

## Major chemical constituents

The major constituent is parthenolide (up to 0.9%), a germacranolide sesquiterpene lactone (*14–16*). Parthenolide and other characteristic sesquiterpene lactones, including members of the guaianolides (e.g. canin and artecanin), contain an α-methylenebutyrolactone structure. To date, more than 45 sesquiterpenes have been identified in Herba Tanaceti Parthenii. Monoterpenes, flavonoids and polyacetylenes have also been detected (*1, 4, 10, 12, 17–19*). The structures of the representative sesquiterpene lactones, parthenolide, 3β-hydroxyparthenolide, canin and artecanin, are presented below.



parthenolide R = H
3β-hydroxyparthenolide R = OH

artecanin

canin

## Medicinal uses

### *Uses supported by clinical data*

Prevention of migraine (*20–24*). Although Herba Tanaceti Parthenii has been used for treatment of rheumatoid arthritis, a clinical study failed to prove any beneficial effects (*25*).

### *Uses described in pharmacopoeias and traditional systems of medicine*

None.

### *Uses described in folk medicine, not supported by experimental or clinical data*

Treatment of anaemia, arthritis, asthma, common cold, constipation, diarrhoea, dysmenorrhoea, dyspepsia, oedema, fever, indigestion, insect bites, rheumatism, sciatica, tinnitus, toothache and vertigo (*4, 26–30*).

## Pharmacology

### *Experimental pharmacology*

#### Prevention and treatment of migraine

The mechanism of action of Herba Tanaceti Parthenii in the prevention of migraine is currently a matter of debate (*27, 31, 32*). However, based on

pharmacological studies of the herb and parthenolide, the mechanism appears to be threefold: antiinflammatory activity, an effect on platelets and inhibition of serotonin binding.

### *Anti-inflammatory activity*

Extracts of the herb and parthenolide both inhibit the biosynthesis of prostaglandins, leukotrienes and thromboxanes, collectively known as eicosanoids, which are potent mediators of inflammation. An aqueous extract of the herb (50 μg/ml) inhibited the activity of lipoxygenase in rat leukocytes in vitro, thereby reducing the biosynthesis of prostaglandins and thromboxane $B_2$ (*33*). A chloroform extract of the leaves ($IC_{50} < 50$ μg/ml) inhibited the biosynthesis in vitro of leukotriene $B_4$ and thromboxane $B_2$ in human and rat leukocytes which had been stimulated by *N*-formyl-methionyl-leucyl-phenylalanine or the calcium ionophore A23187 (*34*). The powdered leaf inhibited arachidonic acid metabolism in *Pseudomonas fluorescens* in vitro (*35*). A buffered aqueous extract of the leaves (pH 7.4) inhibited the activity of phospholipase $A_2$ in human platelets in vitro (30 μl). Phospholipase $A_2$ facilitates the release of arachidonic acid (the precursor of the eicosanoids) from the cell membrane (*36*). The extract was also shown to prevent both arachidonic acid release and metabolism in human platelets in vitro (*36*, *37*). A chloroform–methanol extract of the leaves (100 μl) inhibited the release of vitamin $B_{12}$-binding protein in vitro from human polymorphonuclear leukocytes induced by *N*-formyl-methionyl-leucyl-phenylalanine or sodium arachidonate (*38*). An acetone, chloroform or saline extract of the leaves ($IC_{50}$ 0.79 mg/ml) inhibited oxidative burst in vitro in human polymorphonuclear leukocytes induced by phorbol 12-myristate 13-acetate (*39*, *40*). A chloroform extract of the leaves inhibited histamine release in vitro in rat peritoneal mast cells stimulated by anti-IgE antibodies or the calcium ionophore A23187 (*41*). Parthenolide inhibited gene expression in vitro of cyclooxygenase and the proinflammatory cytokines, tumour necrosis factor-α and interleukin-1, in murine macrophages stimulated by lipopolysaccharide. Parthenolide also suppressed protein tyrosine phosphorylation in these cells, which correlated with its inhibitory effect on the expression of cyclooxygenase and the cytokines (*42*).

### *Effect on platelets*

Another possible mechanism of action of the herb and its constituent sesquiterpene lactones involves the inhibition of platelet aggregation and serotonin release from platelets in response to various chemical stimuli (*27*, *43–45*). Aqueous, chloroform or chloroform–methanol extracts of the leaves (up to 100 μl) inhibited human platelet aggregation in vitro induced by arachidonic acid, collagen or adrenalin (*35*, *36*, *38*, *44*, *46*, *47*). A chloroform extract of the fresh leaves of *Tanaceti parthenium* completely inhibited human platelet aggregation in vitro. After fractionation of the extract, only fractions containing constituents with an α-methylenebutyrolactone functional group were active.

Parthenolide was the most active; canin, tanaparthin-α-peroxide and *cis*-cycloheptane lactone ester were partially active (*48*). Although the exact mechanism by which these compounds affect platelet function is unknown, it has been suggested that their ability to undergo Michael addition with thiol groups may influence their biological activity (*48*). The following evidence supports this hypothesis: addition of cysteine or 2-mercaptoethanol to the crude extract or parthenolide completely suppressed their ability to inhibit platelet aggregation. Furthermore, the inhibitory effects of the extract and parthenolide were both dose- and time-dependent, and treatment of platelets with the extract or parthenolide caused a dramatic reduction in the number of thiol groups (*44, 45, 48*). Acetone, chloroform or chloroform–methanol extracts of the leaves (100 µl) inhibited serotonin release in vitro from human platelets and polymorphonuclear leukocytes stimulated by arachidonic acid, adenosine diphosphate, collagen and adrenalin (*38, 46, 47*). A chloroform–methanol extract did not, however, inhibit serotonin release from human platelets or polymorphonuclear leukocytes stimulated by the calcium ionophore A23187 (*38*). A 95% ethanol extract of the leaves inhibited serotonin release from bovine platelets in vitro ($IC_{50}$ 1.3–2.9 mg/ml) (*49*). The ability of freeze-dried or air-dried aqueous leaf extracts to inhibit serotonin release from human platelets correlated with the concentration of parthenolide in the extracts (*16, 32*).

### *Inhibition of serotonin binding*

Current evidence also indicates that serotonin receptor-based mechanisms are involved in the pathophysiology of migraine. In vitro studies have demonstrated that parthenolide displaces radioligand binding from cloned serotonin receptors and from serotonin receptors isolated from rat and rabbit brains, indicating that parthenolide may be a low-affinity antagonist (*50*).

A chloroform extract of the fresh leaves of *Tanacetum parthenium* inhibited the contractile response of isolated rings of rabbit aorta to exogenously applied serotonin-receptor agonists (serotonin, angiotensin, phenylephrine, thromboxane mimetic U48819 or thromboxane $A_2$) (*51, 52*). However, a chloroform extract of the dried leaves which did not contain parthenolide or other sesquiterpene lactones was not active (*52*).

## Toxicology

An in vitro study demonstrated that an extract of the herb or parthenolide was cytotoxic to human peripheral blood mononuclear cells induced by mitogens and synovial cells stimulated by interleukin-1 (*53*). Parthenolide-induced cytotoxicity was due to the inhibition of thymidine incorporation into DNA (*54, 55*). Intragastric administration of 100 times the normal daily dose for humans of powdered leaf to rats did not result in loss of appetite or weight (*19*).

## *Clinical pharmacology*

### Migraine

Five randomized, double-blind, placebo-controlled studies have assessed the efficacy of various Herba Tanaceti Parthenii products for the prevention of migraine (*21–23, 56, 57*). Three of the trials used an encapsulated dried or freeze-dried leaf product (*21–23*), while one study used a 90% ethanol extract of the herb bound to microcrystalline cellulose (*56*). The remaining study was reported only as an abstract and the herb preparation used was not defined (*57*). These five trials were analysed recently by two independent reviewers (*24*). The data were analysed in a predefined, standardized fashion, and each trial was assessed using the Jadad scoring system. Although the data would suggest that the herb was more effective than a placebo in preventing migraine, a firm conclusion could not be reached given the shortcomings of the trials (such as small sample size, poor definition of inclusion criteria and lack of washout period) (*24*).

In the first study, 17 patients who had been treating themselves with the fresh leaves of *Tanacetum parthenium* for 3–4 years for migraine were recruited. Patients were administered an oral dose of 50 mg (concentration of parthenolide was not stated) of a freeze-dried leaf preparation or a placebo daily for 6 months. The average number of migraines in the treatment group was 1.69 over the whole treatment period and 1.50 during the final 3 months of the study, compared with 3.13 and 3.43, respectively, in the placebo group (*21*). Bouts of nausea and vomiting were reported 39 times in the treatment group, compared with 116 occasions in the placebo group. The reduction in frequency of nausea and vomiting was significant ($P < 0.05$) (*20, 21*).

In the second study, 59 patients with a history of migraine attacks were treated daily with either an encapsulated product containing 70–114 mg leaves (equivalent to 0.545 mg parthenolide) or a placebo, after a 1-month placebo run-in. During this crossover trial, patients received the leaf product for 4 months and then a placebo for 4 months. During the treatment phase, a 24% decrease was reported in the number of migraines in the treatment group as compared with the number in the placebo group. No change in the duration of the migraine or in the proportion of attacks associated with an aura was observed in the treatment group. However, a significant reduction in the number of bouts of nausea and vomiting associated with the migraine was reported ($P < 0.02$). Global assessments of efficacy also demonstrated that the leaf product was significantly superior to the placebo in preventing migraines ($P < 0.0001$) (*22*).

In the third study, 57 patients were divided into two groups for the initial open-label phase. Patients were treated with either a placebo or 100 mg encapsulated leaf preparation (standardized to contain 0.2 mg parthenolide) daily for 60 days. After the open-label phase, a randomized, double-blind, placebo-controlled, crossover study was carried out. Patients were again divided into two groups: 30 patients continued to receive 100 mg leaf preparation and 27 patients received a placebo. After 30 days, the treatments were crossed over (i.e. patients who had

received the placebo were then given the leaf preparation, or vice versa) for a further 30 days. No washout period was allowed between each phase. Results of the open-label phase showed a significant reduction in pain intensity of migraines and symptoms such as vomiting, or sensitivity to light or noise in patients in the treatment group ($P < 0.001$). In the double-blind phase, patients in the treatment group reported a significant decrease in the pain intensity of migraines ($P < 0.01$), while patients in the placebo group noted an increase. Similar results were reported after the crossover. In the double-blind phase, a significant decrease in vomiting ($P < 0.001$) and light- and noise-sensitivity ($P < 0.017$) was observed in the treatment group compared with the placebo group (*23*).

A randomized, double-blind, placebo-controlled, crossover study assessed the efficacy of a 90% ethanol extract of the herb bound to microcrystalline cellulose in the prevention of migraine headache in 44 patients. Diagnosis was carried out using the International Headache Society diagnostic criteria. After an initial 1-month placebo run-in, patients were treated with either 143 mg extract standardized to contain 0.5 mg parthenolide or placebo daily for 4 months, then the treatments were crossed over for a further 4 months (*56*). The average response to the two treatments was the same and the extract did not prevent migraines. Statistical significance was not reported.

A study without controls demonstrated that platelet aggregation in 10 patients who had taken preparations of the herb for 3.5–8.0 years was the same as in a control group of four patients who had stopped taking the herb for at least 6 months prior to being tested (*58*).

### Rheumatoid arthritis

A double-blind, placebo-controlled trial assessed the efficacy of the herb for the treatment of rheumatoid arthritis. Forty women with rheumatoid arthritis were treated with either 70–86 mg of an encapsulated leaf product or a placebo daily for 6 weeks. No beneficial effects were observed (*25*).

## Contraindications

Herba Tanaceti Parthenii is contraindicated in cases of known allergy to plants of the Asteraceae family, and during pregnancy (*1*, *19*, *28*).

## Warnings

No information available.

## Precautions

### *Carcinogenesis, mutagenesis, impairment of fertility*

No significant differences were observed in the mean frequency of chromosomal aberrations or sister-chromatid exchange in the circulating peripheral lym-

phocytes of 30 patients who had taken Herba Tanaceti Parthenii for 11 months or longer. Urine samples from these patients did not induce a significant increase in the number of revertants in the *Salmonella*/microsome assay with or without metabolic activation (*59*).

### *Pregnancy: teratogenic effects*

See Contraindications. The use of Herba Tanaceti Parthenii during pregnancy is contraindicated due to its uterotonic activity in vivo (*19*, *28*).

### *Pregnancy: non-teratogenic effects*

See Contraindications.

### *Other precautions*

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; nursing mothers; or paediatric use. Therefore, Herba Tanaceti Parthenii should not be administered during lactation or to children without medical supervision.

## Adverse reactions

Dizziness, heartburn, indigestion, inflammation of the mouth and tongue with swelling of the lips, loss of taste, mouth ulceration, and weight gain have been reported (*19*, *21*, *22*). Mouth ulceration is a systemic reaction to Herba Tanaceti Parthenii and requires discontinuation of the product. Inflammation of the mouth and tongue with swelling of the lips appears to be a local reaction that may be overcome by using encapsulated herb products. Abdominal bloating, heart palpitations, constipation, diarrhoea, flatulence, increased menstrual flow, nausea and skin rashes have also been reported to a lesser degree (*21*, *22*, *56*). Allergic reactions, such as contact dermatitis, have also been reported (*19*). Cross-sensitivity between pollen allergens of other members of the Compositae family, *Parthenium hysterophorus* (American feverfew) and *Ambrosia* species (ragweed), has been reported (*60*).

## Dosage forms

Crude drug for decoction; powdered drug or extracts in capsules, tablets, tinctures and drops (*2*). Store in a well-closed container, protected from light and humidity (3).

## Posology

(Unless otherwise indicated)
Daily dosage: encapsulated crude drug equivalent to 0.2–0.6 mg parthenolide (as a chemical marker) for prevention of migraine (*21–23*, *27*, *32*).

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# Radix Urticae

## Definition

Radix Urticae consists of the dried roots and rhizomes of *Urtica dioica* L., *U. urens* L. (Urticaceae), their hybrids or mixtures thereof (*1*, *2*).

## Synonyms

### *Urtica dioica L.*

*Urtica gracilis* Ait., *U. major* Kanitz., *U. urens maxima* Blackw. (3, *4*).

### *Urtica urens L.*

*Urtica minor* Fuchs, *U. minor* Moench., *U. urens minima* Dod. (3, *4*).

## Selected vernacular names

### *Urtica dioica L.*

Brennesselwurzel, common nettle, csalángyökér, gazaneh, grande ortie, greater nettle, grosse Brennessel, Haarnesselwurzel, Hanfnesselwurzel, hhurrayq, Nesselwurzel, nettle root, ortica, ortie, ortiga, pokrzywa, qurrays, racine d'ortie, raiz de ortiga, stinging nettle, tsuknida, zwyczajna (*4–6*).

### *Urtica urens L.*

Dwarf nettle, Eiternessel, kleine Brennessel, lesser nettle, ortica minore, ortica piccola, ortie brulante, petite ortie, sha'reláguz, small nettle (*4*, *6–9*).

## Geographical distribution

*Urtica dioica* is indigenous to Africa and western Asia, but is now found in all temperate regions of the world in Africa, North and South America, Asia, Australia and Europe (3, *4*, *6*, *7*, *10*).

Owing to the difficulty in botanical differentiation between *Urtica dioica* and *U. urens* in the wild, they are often harvested together. Although both species have a similar distribution, *U. urens* has become less widely distributed due to the reduction of its habitat (3).

## Description

### *Urtica dioica L.*

A herbaceous perennial with erect, green to purplish square stems, 30–150 cm high, with creeping roots; whole plant covered with stinging hairs. Leaves opposite, cordate at the base, oblong or ovate, finely toothed; upper surface dark green and underside paler. Flowers incomplete, small, green, dioecious (plant has either male or female flowers in separate inflorescences) and occur as racemes in axils of upper leaves; male or barren flowers have a perianth of 4 segments and 4 stamens, which are bent inwards at bud stage; female or fertile flowers have similar perianth surrounding a single 1-seeded carpel, bearing 1 style with a brush-like stigma. Fruit an achene (*3*, *8*).

### *Urtica urens L.*

A herbaceous annual resembling *Urtica dioica*, but is smaller (usually up to 30 cm high), has smaller leaves and flowers are in short, mostly unbranched clusters; male and female flowers appear together in the same raceme. Glabrous except for the stinging hairs (*8*, *11*).

## Plant material of interest: dried roots and rhizomes

### *General appearance*

Rhizome cylindrical and tapering, occasionally branched, up to about 6 mm thick at upper end; outer surface yellowish-brown; internodes with deep longitudinal furrows, numerous smooth, very thin and wiry roots arising from the nodes; in the outer part, inner surface creamy-white with a central hollow; fracture fibrous and tough.

Root greyish-brown, irregularly twisted, about 5 mm thick, distinct longitudinal furrows; hollow in cross-section, cut surface white; fracture fibrous and tough (*1*, *7*).

### *Organoleptic properties*

Odourless; taste: faintly aromatic, characteristically bitter (*1*).

### *Microscopic characteristics*

Rhizome: thin cork composed of brown, thin-walled cells, a few rows of tangentially elongated cortical parenchyma and a pericyclic region with fairly numerous fibres; fibres usually in small groups, sometimes single; individual fibres greatly elongated with very thick, lignified walls; some cells of pericycle and outer part of the secondary phloem contain fairly large cluster crystals of calcium oxalate. Cambial region distinct and continuous, with narrow radial groups of vascular tissues separated by wide medullary rays; secondary phloem

mainly parenchymatous, whereas secondary xylem dense and completely lignified; medullary rays in secondary xylem show alternating areas of lignified and unlignified cells; lignified cells have moderately thickened walls and numerous simple pits. Pith composed of rounded, unlignified parenchyma.

Root: very thin cork, narrow phelloderm and secondary phloem and xylem with alternating areas of lignified and unlignified parenchyma in the wide medullary rays, as in the rhizome; a strand of primary xylem in the centre with a few small vessels (*1*).

### *Powdered plant material*

Fibrous and pale beige. Fragments of greatly elongated pericyclic fibres, occurring singly or in groups, with thick and lignified walls, xylem vessels with bordered pits, associated with thick-walled fibres with slit-shaped pits; lignified, moderately thick-walled and pitted parenchyma from the medullary rays of xylem; abundant thin-walled parenchymatous cells, some containing large cluster crystals or scattered crystals of calcium oxalate; fragments of brownish cork (*1*).

## General identity tests

Macroscopic and microscopic examinations (*1*, *2*), and thin-layer chromatography for scopoletin and phytosterols (*2*).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

### *Foreign matter*

Not more than 2% (*1*).

### *Total ash*

Not more than 8% (*2*).

### *Acid-insoluble ash*

Not more than 3.5% (*1*).

### *Water-soluble extractive*

Not less than 15% (*1*).

### Loss on drying

Not more than 12% (*2*).

### Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*), and pesticide residues (*14*).

### Heavy metals

For maximum limits and analysis for heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

### Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

### Other purity tests

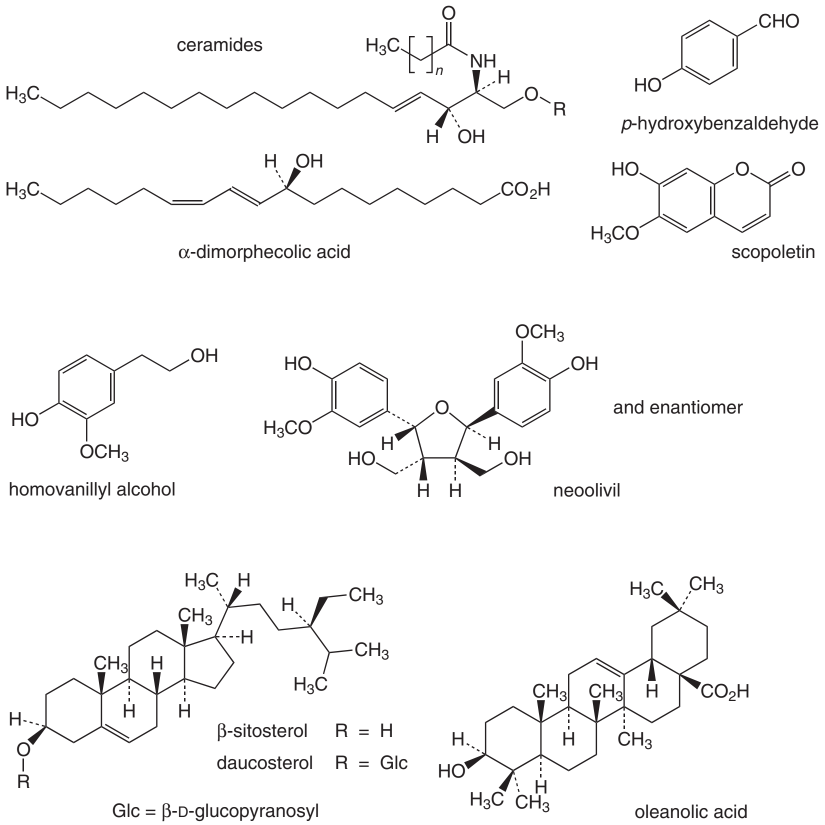
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

## Chemical assays

In addition to thin-layer chromatography for qualitative analysis (*2*), enzyme-linked immunosorbent assay and high-performance liquid chromatography methods have also been developed to determine the concentration of *Urtica dioica* agglutinin in Radix Urticae (*15, 16*). However, concentration limits need to be established.

## Major chemical constituents

A large number of compounds of different polarity and belonging to various chemical classes, including fatty acids, terpenes, phenylpropanes, lignans, coumarins, triterpenes, ceramides, sterols and lectins, have been isolated from Radix Urticae. Among these are oxalic acid, linoleic acid, 14-octacosanol, 13-hydroxy-9-*cis*,11-*trans*-octadecadienoic acid, α-dimorphecolic acid (9-hydroxy-10-*trans*,12-*cis*-octadecadienoic acid), scopoletin, *p*-hydroxybenzaldehyde, homovanillyl alcohol, β-sitosterol, stigmasterol, 24-*R*-ethyl-5α-cholestan-3β,6α-diol, campesterol, daucosterol (and related glycosides), secoisolariciresinol-9-*O*-β-D-glucoside, neoolivil, oleanolic acid, ursolic acid, *Urtica dioica* agglutinin and polysaccharides RP1–RP5 (*3–5, 10, 17–21*). The structures of the representative constituents are presented below.




# Medicinal uses

## Uses supported by clinical data

Symptomatic treatment of lower urinary tract disorders (nocturia, polyuria, urinary retention) resulting from BPH stages I and II, as defined by Alken, in cases where diagnosis of prostate cancer is negative (*22–35*).

## Uses described in pharmacopoeias and traditional systems of medicine

As a diuretic and for the treatment of rheumatism and sciatica (*6*).

## Uses described in folk medicine, not supported by experimental or clinical data

Treatment of asthma, coughs, dandruff, diabetes, diarrhoea, eczema, fever, gout, haemorrhoids, nose bleeds, scurvy, snakebites and tuberculosis (*5*, *6*). The

plant has also been used to stop uterine bleeding after childbirth, increase lactation and promote hair growth, and as a vermifuge (*5, 6*).

## Pharmacology

### *Experimental pharmacology*

#### Anti-inflammatory activity

An ethanol extract of Radix Urticae inhibited the activity of human leukocyte elastase and reduced the amount of the enzyme released by activated polymorphonuclear granulocytes during the inflammatory response. The extract also inhibited degradation of a peptide substrate in vitro by human leukocyte elastase ($IC_{50}$ 3.6 μg/ml) and bovine elastin ($IC_{50}$ 68 μg/ml) (*36*). Intragastric administration of a polysaccharide fraction isolated from Radix Urticae to rats (40 mg/kg body weight) suppressed carrageenan-induced footpad oedema for up to 20 h (*21, 37*). The activity of the polysaccharides was comparable to that of indometacin (10 mg/kg body weight) (*21, 37*).

#### Lymphocyte proliferation

A lyophilized aqueous extract (10 μg/ml) and a 40% alcohol extract of the roots (100 μg/ml) stimulated human lymphocyte proliferation in vitro by 63% and 100%, respectively (*21, 37*). Polysaccharides isolated from an aqueous root extract induced human lymphocyte proliferation in vitro (10–100 μg/ml) (*21, 37*). An ethyl acetate extract of the roots induced cell differentiation in human promyelocytic leukaemia HL-60 cells in vitro ($ED_{50}$ 4 μg/ml) (*38*). *Urtica dioica* agglutinin (500 ng/ml), however, inhibited lymphocyte proliferation and the binding of epidermal growth factor to its receptor on A431 epidermoid cancer cells in vitro (*39*). The lectin also exhibited immunomodulatory effects on T-lymphocytes in a dose-dependent manner (*21, 37*). *Urtica dioica* agglutinin bound to the cell membrane of prostatic hyperplastic cells (*40*) and inhibited their proliferation (*21*).

#### Effect on benign prostatic hyperplasia

##### *Effect on sex hormone-binding globulin*

Sex hormone-binding globulin (SHBG) is a blood plasma protein that binds to circulating androgens and estrogens, thereby regulating their free concentration in plasma. The plasma membrane of the human prostate contains specific SHBG receptors, and SHBG appears to play a role in the development of BPH. A 10% hydroalcoholic extract of the root reduced the binding capacity of SHBG (isolated from human plasma) for 5α-dihydrotestosterone by 67% in vitro (*41*). An aqueous extract of the root (0.6–10.0 mg/ml) inhibited the binding of $^{125}$I-labelled SHBG to human prostate membranes in vitro (*42*). The lignan, secoisolariciresinol, and a mixture of the isomeric compounds 13-hydroxy-9-*cis*,11-*trans*-octadecadienoic acid and 9-hydroxy-10-*trans*,12-*cis*-octadecadienoic acid isolated from a methanol root extract, reduced the binding of SHBG to 5α-

dihydrotestosterone (*18*). Secoisolariciresinol and its main intestinal transformation products, (–)-3,4-divanillyltetrahydrofuran and enterofuran, displaced the binding of 5α-dihydrotestosterone to SHBG in vitro by 60%, 95% and 73%, respectively (*43*).

### *Enzymatic activity*

Intragastric administration of a 30% ethanol extract of the root to male mice inhibited the activities of 5α-reductase and aromatase ($ED_{50}$ 14.7 and 3.58 mg/ml, respectively) (*44*). However, a hydroalcoholic extract of the root dissolved in dimethyl sulfoxide did not inhibit the activity of 5α-reductase from human prostate cells in vitro (up to 500 μg/ml) (*45*). A standardized hydroalcoholic extract of the roots ($IC_{50}$ 338 μg/ml) inhibited aromatase activity in vitro. A heptane-soluble fraction of the extract was the most effective inhibitor ($IC_{50}$ 9 μg/ml) (*36*). Both ursolic acid and 14-octacosanol isolated from a methanol extract of the roots inhibited the activity of aromatase in vitro (*46*). 9-Hydroxy-10-*trans*,12-*cis*-octadecadienoic acid isolated from the roots inhibited the activity of aromatase in vitro (*19*). Butanol, ether, ethyl acetate and hexane extracts of the roots inhibited the activity of sodium- and potassium-adenosine triphosphatase isolated from prostatic hyperplastic cells by 27.6–81.5% (*47*). In addition, steroidal components of the roots, stigmast-4-en-3-one, stigmasterol and campesterol (1 μmol/l to 1 mmol/l), inhibited sodium- and potassium-adenosine triphosphatase activity by 23–67% (*47*).

### *Effect on prostate growth*

Intragastric administration of a hexane extract of the roots (1.28 g daily) to castrated rats did not inhibit prostate growth stimulated by testosterone or dihydrotestosterone (*45*). Intraperitoneal administration of a hydroalcoholic extract of the roots (20 mg/kg body weight) suppressed testosterone-stimulated increases in prostate weight and prostatic ornithine decarboxylase activity in castrated rats (*48*). Daily oral administration of a hydroalcoholic extract of the root to dogs with BPH (30 mg/kg body weight) decreased prostate volume by 30% after 100 days of treatment (*49*).

The effect of various root extracts was assessed after implantation of the fetal urogenital sinus into the prostate gland of adult mice. Intragastric administration of a butanol, cyclohexane or ethyl acetate extract of the root (0.25 ml/daily for 3 weeks) had no effect on the development of BPH in mice. However, intragastric administration of the same dose of a 20% methanol extract of the root reduced the development of BPH by 51.4% (*50*).

## Toxicology

The $LD_{50}$ of an aqueous extract or infusion of the roots after intravenous administration to rats was 1721 mg/kg body weight and 1929 mg/kg body weight,

respectively. Oral administration of an infusion of the roots to rats was well tolerated at doses up to 1310 mg/kg body weight (*3*).

## Clinical pharmacology

### Benign prostatic hyperplasia

#### Placebo-controlled clinical trials

Three double-blind, placebo-controlled clinical trials have assessed the efficacy of oral administration of Radix Urticae for the symptomatic treatment of lower urinary tract disorders resulting from BPH (*24*, *27*, *35*). One study assessed the efficacy of a 20% methanol extract of the roots in 50 men with BPH stages I and II (*35*). A significant increase in urine volume (by 43.7%; $P = 0.027$) and a significant decrease in serum levels of SHBG ($P = 0.0005$) was observed in patients treated with 600 mg extract daily for 9 weeks. A modest increase in maximum urinary flow of 8% was also observed in the treated group; however, it was not significant (*35*). Another study assessed the efficacy of a 20% methanol extract in 40 men with BPH. Treatment with 1200 mg extract daily for 6 weeks decreased the frequency of micturition and serum levels of SHBG (*27*). The third study assessed the efficacy of a methanol extract in the treatment of 32 men with BPH stage I (*24*). A 4–14% increase in average urinary flow and a 40–53% decrease in postvoid residual volume were observed in patients treated with 600 mg extract daily for 4–6 weeks (*24*).

#### Clinical trials without controls

Numerous clinical trials without controls have assessed the efficacy of oral administration of various Radix Urticae extracts (20% methanol or 30–45% ethanol) for the symptomatic treatment of lower urinary tract disorders (nocturia, polyuria, dysuria, urine retention) resulting from BPH (*22*, *23*, *25*, *26*, *28–32*, *34*, *51*, *52*). One trial assessed the efficacy of a 40% ethanol extract of the roots in 67 men with BPH. Treatment with 5 ml daily for 6 months decreased nocturia and postvoid residual volume, but did not reduce prostate enlargement (*23*). In another trial, a 20% methanol extract of the roots was assessed in 89 men with BPH. Treatment with 600 mg daily decreased the postvoid residual volume in 75% of patients after 3–24 months (*25*). In a study of 26 men with BPH stage I or II, a decrease in prostate volume was observed in 54% of patients, and a decrease in postvoid residual volume was observed in 75% of patients, after treatment with 1200 mg methanol extract daily for 3–24 weeks (*26*). Ten men with BPH were treated with 30–150 drops of a 45% ethanol extract of the root daily for 30 days. After treatment, the postvoid residual volume decreased by 66% (*29*). In a study of 39 men with BPH stages I–III, an improvement in urinary flow, and a reduction in postvoid residual volume, nocturia and polyuria were seen in 95% of patients after 6 months of treatment with a 20% methanol extract (600–1200 mg daily) (*51*). Twenty-seven men with BPH stages I and II were treated with a 20% methanol extract of the roots for 3.5 months. Postvoid residual volume decreased significantly in 75%

of patients ($P < 0.001$), and maximum urinary flow increased significantly in 50% of patients ($P < 0.002$) (*52*).

Three large-scale multicentre studies involving 14 033 men with BPH assessed the efficacy of a 20% methanol extract (*28*, *31*, *32*). In one study, a decrease in nocturia and polyuria was seen in 91% of patients after 6 months of treatment (*28*). In another study, a 50% decrease in nocturia was observed in patients treated with 1200 mg extract daily for 10 weeks (*31*). In the third study, significant improvements in both urinary flow and postvoid residual volume were observed in 4480 patients treated with 600–1200 mg extract daily for 20 weeks ($P < 0.01$) (*32*).

***Effects on prostate morphology***

Three studies without controls examined the effect of various methanol extracts of Radix Urticae on prostate morphology. Prostate cells were obtained from patients with BPH by needle biopsy, and were analysed for morphological changes before and after treatment. In two of the studies, cells were taken from the patients at various intervals during treatment (*53*, *54*). In the third study, cells were obtained once from the patients, and treatment with the extract was carried out in vitro (*55*). In the first study, 31 men with BPH stages I and II were treated orally with 1200 mg of a 20% methanol root extract daily for 20 weeks. Prostate cells were analysed every 4 weeks by fluorescent microscopy. After 4–16 weeks of treatment, an increase in nuclear volume, as well as hydropic swelling and vacuolization of the cytoplasm, were observed (*53*). In the second study, prostate cells from four men with BPH stage I were examined by electron microscopy. After 6 months of oral treatment with a 20% methanol extract (1200 mg daily), a reduction in the activity of smooth muscle cells and an increase in the secretory activity of glandular epithelial cells were observed (*54*). In the third study, prostate glandular epithelial cells from 33 patients with BPH were analysed by fluorescent microscopy following incubation of the cells in vitro with a 20% methanol extract of the root. Treatment with the extract caused an increase in nuclear volume, loosening of chromatin and hydropic swelling of the cytoplasm. In addition, the number of homogeneous secretory granules was reduced, indicating a reduction in the biological activity of these cells (*55*).

## Contraindications

Radix Urticae is contraindicated in cases of known allergy to plants of the Urticaceae family. Owing to its effects on androgen and estrogen metabolism, the use of Radix Urticae during pregnancy and lactation and in children under the age of 12 years is contraindicated.

## Warnings

Radix Urticae relieves the symptoms associated with BPH but does not have an effect on the size of the prostate. If symptoms worsen or do not

improve, or in cases of blood in the urine or acute urinary retention, contact a physician.

## Precautions

### *Pregnancy: teratogenic effects*

See Contraindications.

### *Pregnancy: non-teratogenic effects*

See Contraindications.

### *Nursing mothers*

See Contraindications.

### *Paediatric use*

See Contraindications.

### *Other precautions*

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; or carcinogenesis, mutagenesis and impairment of fertility.

## Adverse reactions

Clinical studies have shown that extracts of Radix Urticae are well tolerated in humans. A few cases of minor transient gastrointestinal side-effects, such as diarrhoea, gastric pain and nausea (*32, 35*), and allergic skin reactions (*32*), have been reported.

## Dosage forms

Crude drug for infusion; hydroalcoholic extracts (*4, 56*). Store in a well-closed container, protected from light and humidity (*2, 13*).

## Posology

(Unless otherwise indicated)
Daily dosage: 4–6 g crude drug or equivalent preparations as an infusion (*4, 56*); 600–1200 mg dried 20% methanol extract (5 : 1) (*22, 25, 27, 31, 32*); 1.5–7.5 ml 45% ethanol extract (1 : 1) (*29*); 5 ml 40% ethanol extract (1 : 5) (*17, 23*).

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# Folium Uvae Ursi

## Definition

Folium Uvae Ursi consists of the dried leaves of *Arctostaphylos uva-ursi* (L.) Spreng. (Ericaceae) (*1–3*).

## Synonyms

*Arbutus uva-ursi* L., *Arctostaphylos media* Greene, *Arctostaphylos officinalis* Wimm., *Arctostaphylos procumbens* Patzke, *Mairania uva-ursi* Desv., *Uva-ursi buxifolia* S.F. Gray, *Uva-ursi procumbens* Moench. (*4*).

## Selected vernacular names

Achelblätter, Achelkraut, arberry, arctostaphylos, Bärenkraut, Bärentraube, Bärentraubenblätter, bearberry, bear's grape, Beredruif, berry leaves, brockberry, busserole, coralillo, crowberry, dogberry, enab edhdhib, feuille de busserole, feuille de raisin d'ours, folia artostaphyli, folia garjubae, folia uvae-ursi, folia vaccinii ursi, foxberry, gayuba, herba garjubae, hog cranberry, hojas de gayuba, kinnikinnick, leesikas, lisc maçznicy, mealyberry, medveszölölevel, Moosbeerenblätter, mountain box, ptarmigan berry, raisin d'ours, red bearberry, sagochomi, Sandblätter, Steinbeerenblätter, upland cranberry, uva ursi, uvaursina, uwaurushi, Wolfsbeerenblätter (*4–6*).

## Geographical distribution

Found in North America, Asia and northern Europe (*6*).

## Description

Procumbent evergreen shrub with trailing stems bearing short ascending branches; branches bear leaves that are ovate, ovate-spatulate to spatulate. Flowers bell-shaped, pinkish-white, hypogynous and borne in small clusters at ends of branches; each flower consists of a calyx of 5 reddish sepals, a reddish-white urceolate corolla, gamopetalous but divided at the margin into 5 short reflexed segments, 10 short stamens with 2-lobed anthers, and syncarpous pistil of 5 carpels. Style portion of the pistil simple, longer than the stamens and ends in a knob-like stigma (*6*).

## Plant material of interest: dried leaves

### *General appearance*

Leaf entire or nearly entire; lamina obovate, oblong or spatulate, 7–30 mm long and 5–13 mm wide, apex obtuse or rounded, margin entire or slightly revolute, base cuneate, tapering to a short (about 5 mm long), slightly pubescent petiole. Upper surface green to brownish-green, waxy, shiny and coriaceous, finely wrinkled due to depression of midrib and veins. Lower surface greyish-green, reticulate. Young leaves ciliate on the margins, old leaves glabrous (*1*, *3*, *6*).

### *Organoleptic properties*

Odour: slightly aromatic, tea-like; taste: astringent, bitter (*1*, *6*).

### *Microscopic characteristics*

Both epidermises covered with a thick cuticle; cells of the upper epidermis rectangular with straight, slightly thickened and distinctly pitted and beaded walls; cells of the lower epidermis similar but smaller; numerous large, anomocytic stomata in lower epidermis only. Occasional unicellular, thick-walled, conical trichomes on petiole and margin of young leaves; palisade usually of 3 layers, occasionally more; some spongy mesophyll cells filled with orange-brown pigment; prismatic crystals of calcium oxalate in parenchymatous cells surrounding the narrow, lignified sclerenchymatous fibres associated with the veins (*1*).

### *Powdered plant material*

Greenish-grey or yellowish-green. Numerous cells of the mesophyll with chloroplasts and frequently irregular masses of carbohydrate; fragments of fibrovascular bundles showing spiral tracheae and narrow lignified sclerenchyma fibres associated with crystal fibres containing monoclinic prismatic crystals of calcium oxalate up to 30 μm in length; epidermis with polygonal cells and broadly elliptical anomocytic stomata up to 40 μm in length, surrounded by 5–11 subsidiary cells; pericyclic fibres lignified, of irregular shape with thick, porous, tuberculated walls and curved ends; trichomes unicellular, non-glandular, short, serpentine or straight; numerous fragments of cells containing yellowish-brown resin which turns blueish-black with iron (III) chloride test solution (*3*, *6*).

## General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for the presence of arbutin, hydroquinone and gallic acid (*2*, *3*).

## Purity tests

### Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*7*).

### Foreign organic matter

Not more than 5% twigs and not more than 3% other foreign matter (*2*, *3*).

### Total ash

Not more than 5% (*2*, *3*).

### Acid-insoluble ash

Not more than 1.5% (*2*).

### Water-soluble extractive

Not less than 25% (*1*).

### Loss on drying

Not more than 10% (*3*).

### Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*3*). For other pesticides, see the *European pharmacopoeia* (*3*), and the WHO guidelines on quality control methods for medicinal plants (*7*) and pesticide residues (*8*).

### Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*7*).

### Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*7*) for the analysis of radioactive isotopes.

### Other purity tests

Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

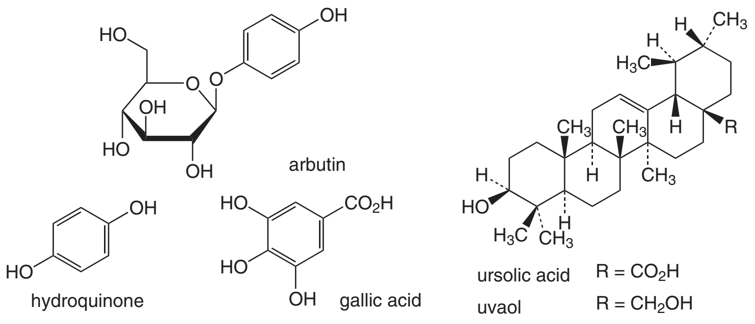
## Chemical assays

Contains not less than 7% hydroquinone derivatives calculated as anhydrous arbutin, according to *The Japanese pharmacopoeia* (*2*). Contains not less than 8%

hydroquinone derivatives calculated as anhydrous arbutin, according to the *European pharmacopoeia* (*3*). Quantitative analysis is performed by spectrophotometry at 455 nm (*3*) or by high-performance liquid chromatography for the quantitative analysis of arbutin (*2*), hydroquinone and related derivatives (*9*).

## Major chemical constituents

The major constituent is arbutin (5–15%). Related hydroquinone derivatives present include hydroquinone and methylarbutin (up to 4%). Gallic acid is the major phenolic carboxylic acid present, together with galloyl arbutin and up to 20% of gallotannins, flavonoids and triterpenes, mainly ursolic acid and uvaol (*4, 10–12*). The structures of the major constituents are presented below.




## Medicinal uses

### *Uses supported by clinical data*

None.

### *Uses described in pharmacopoeias and in traditional systems of medicine*

Internally, as a mild urinary antiseptic for moderate inflammatory conditions of the urinary tract and bladder, such as cystitis, urethritis and dysuria (*11, 13, 14*).

### *Uses described in folk medicine, not supported by experimental or clinical data*

As a diuretic, to stimulate uterine contractions, and to treat diabetes, poor eyesight, renal or urinary calculi, rheumatism and venereal disease (*4, 5, 15*). Topical applications have been used for skin depigmentation (*15*).

## Pharmacology

### *Experimental pharmacology*

#### Antimicrobial activity

A 30% ethanol extract of Folium Uvae Ursi inhibited the growth in vitro of *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Serratia marcescens* and *Staphylococcus aureus* (*16*). However, 95% ethanol or chloroform extracts had no antibacterial activity (*17, 18*). An aqueous extract of the leaves inhibited the growth of *Streptococcus mutans* OMZ176 in vitro (*19*). Ethanol and ethyl acetate extracts of the leaves were active in vitro against *Escherichia coli*, *Proteus vulgaris*, *Streptococcus faecalis* and *Enterobacter aerogenes* (*20*). Arbutin is responsible for most of the antibacterial activity (*21*). Arbutin and hydroquinone inhibited the growth in vitro of *Ureaplasma urealyticum* and *Mycoplasma hominis* (*22*). After ingestion of the leaves, arbutin is absorbed from the gastrointestinal tract, and is hydrolysed by intestinal flora to form the aglycone, hydroquinone (*23*). Hydroquinone is metabolized to glucuronate and sulfate esters that are excreted in the urine (*24, 25*). These active hydroquinone derivatives exert an antiseptic and astringent effect on the urinary mucous membranes when the urine is alkaline (pH 8.0). Their antibacterial action reaches a maximum approximately 3–4 hours after ingestion (*13*).

An aqueous extract of the leaves had antiviral activity in vitro against herpes simplex virus type 2, influenza virus A2 (Mannheim 57) and vaccinia virus at a concentration of 10% (*26*).

#### Anti-inflammatory activity

Intragastric administration of a 50% methanol extract of the leaves (100 mg/kg body weight) to mice inhibited picryl chloride-induced ear inflammation (*27*). The extract also potentiated the efficacy of prednisolone and dexamethasone in mice (*27, 28*). Arbutin, however, had no effect on the activity of the two steroids (*28*).

#### Effect on glucose levels

Administration of the leaves (6.35% of diet) to streptozocin-treated mice for 18 days did not reduce plasma glucose levels (*29*).

#### Effect on calcium excretion

Addition of an infusion of the leaves to the drinking-water (3 g/l) of rats fed a standard diet fortified with calcium (8 g/kg body weight) had no effect on urinary calcium excretion and diuresis (*30*).

#### Antitussive activity

Arbutin (50–100 mg/kg body weight, administered intraperitoneally or intragastrically) was as active as codeine (10 mg/kg body weight, administered

intraperitoneally) as an antitussive in unanaesthetized cats with coughs induced by nylon fibres (*31*).

### Effect on skin depigmentation

Extracts of the leaves have been widely used in cosmetic preparations to lighten the skin, with the active principles being hydroquinone and its derivatives (*15*).

### Toxicity and overdose

The oral $LD_{50}$ of hydroquinone ranged from 300 to 1300 mg/kg body weight in rodents and dogs, but was only 42–86 mg/kg body weight in cats. Acute exposure of rats to high doses of hydroquinone (over 1300 mg/kg body weight) caused severe effects on the central nervous system, including hyperexcitability, tremor, convulsions, coma and death (*32*).

## *Clinical pharmacology*

### Antibacterial activity

In a study without controls, urine samples from healthy volunteers were collected 3 hours after oral administration of 0.1 or 1.0 g arbutin. The urine samples (adjusted to pH 8.0) and 20 antibacterial compounds (at their usual urine concentration) were tested in vitro using 74 strains of bacteria, including *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Only arbutin (present in urine samples collected after administration of 1.0 g arbutin), gentamicin and nalidixic acid were active against all the strains tested (*24*). Oral administration of 800 mg arbutin or an infusion of the leaves containing an equivalent amount of arbutin to healthy volunteers had strong antibacterial activity, as measured in urine samples after adjustment of the urine pH to 8.0 (*25*).

# Contraindications

During pregnancy (*33*) or lactation, or in children under the age of 12 years (*13*). Folium Uvae Ursi is also contraindicated in patients with kidney disorders (*12*).

# Warnings

Folium Uvae Ursi should not be used for prolonged periods. Patients with persistent symptoms of a urinary tract infection should consult a physician. Use of Folium Uvae Ursi may cause a greenish-brown coloration of the urine that darkens on exposure to air due to the oxidation of hydroquinone.

# Precautions

## *Drug interactions*

Folium Uvae Ursi should not be administered with foods or medicines that acidify the urine.

### Carcinogenesis, mutagenesis, impairment of fertility

Folium Uvae Ursi was not mutagenic in the *Salmonella*/microsome assay with *S. typhimurium* strains TA98 or TA100 (*34, 35*). Hydroquinone was also not mutagenic in the *Salmonella*/microsome assay with *S. typhimurium* strains TA98, TA100, TA1535 or TA1537, with or without metabolic activation (*36*).

Although extracts of the leaves do not appear to be carcinogenic, there is some evidence that hydroquinone is carcinogenic. Treatment of F344/N rats with hydroquinone resulted in a marked increase in tubular cell adenomas of the kidney in males, and an increase in mononuclear cell leukaemia in females. There was also some evidence of carcinogenic activity of hydroquinone in female B6C3F$_1$ mice, as shown by an increase in hepatocellular neoplasms, mainly adenomas. There was no evidence, however, of carcinogenic activity of an aqueous extract of the leaves in male B6C3F$_1$ mice (treated by gavage with 50–100 mg extract/kg body weight) (*36*). The sources of human exposure to hydroquinone (including environmental sources) have been reviewed, as have data on its kinetics and metabolism, and its effects in animals and humans (*32*).

Arbutin was administered subcutaneously at 25, 100 or 400 mg/kg body weight daily to male rats before mating, and to female rats during pregnancy and lactation. No effect on reproduction of male and female rats, or the development of the offspring was observed at doses of up to 100 mg/kg body weight. Fetal toxicity was observed at doses of 400 mg/kg body weight (*37*).

### Pregnancy: teratogenic effects

See Contraindications.

### Pregnancy: non-teratogenic effects

See Contraindications.

### Nursing mothers

See Contraindications.

### Paediatric use

See Contraindications.

### Other precautions

No information available on general precautions or precautions concerning drug interactions; or drug and laboratory test interactions.

## Adverse reactions

Internal use of Folium Uvae Ursi may cause nausea and vomiting due to stomach irritation from the high tannin content (*13, 38*). The hydroquinone concentration in topical preparations is limited to 2% in Nigeria, the United

Kingdom and the United States of America, following reports that preparations containing more than 2% hydroquinone caused exogenous ochronosis in black women in South Africa (*39*). Topical application of preparations containing less than 3% hydroquinone in different bases caused negligible effects in male volunteers from different racial groups. However, there are case reports suggesting that skin-lightening creams containing 2% hydroquinone have produced leukoderma as well as ochronosis. Hydroquinone (at a concentration of 1% in aqueous solution or 5% in a cream) has caused erythema and allergic contact dermatitis (*32*).

## Dosage forms

Crude drug for infusions or cold macerates, extracts and solid forms for oral administration (*13*). Store in a well-closed container, protected from light (*3*).

## Posology

(Unless otherwise indicated)
Daily dose: 3 g crude drug in 150 ml water as an infusion or cold macerate, up to three or four times daily; 400–850 mg hydroquinone derivatives. Other preparations accordingly calculated as arbutin (*12, 13*).

Patients should avoid highly acidic foods, such as acidic fruits or fruit juice, during treatment (*25, 40*), and be advised to drink plenty of fluids.

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# Annex 1

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# Annex 2

## Cumulative index (*in alphabetical order of plant name*)

For the convenience of users of volume 2, the monographs described in volume 1 are also listed in this index. The numbers printed in bold type, preceding the page numbers, indicate the volume in which the indexed item is to be found. **Monographs are listed in alphabetical order of the plant name.**


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## Cumulative index (*in alphabetical order of plant material of interest*)

For the convenience of users of volume 2, the monographs described in volume 1 are also listed in this index. The numbers printed in bold type, preceding the page numbers, indicate the volume in which the indexed item is to be found. **Monographs are listed in alphabetical order of the plant material of interest.**


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